INSIDE STANFORD MEDICINE

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The city of Palo Alto recognized medical student Laura Lu for helping to save a man's life with CPR.

Page 4

A step toward gene therapy for sickle cell

By Jennie Dusheck

A team of researchers at the School of Medicine has used a gene-editing tool known as CRISPR to repair the gene that causes sickle cell disease in human stem cells, which they say is a key step toward developing a gene therapy for the disorder.

The team went on to demonstrate that the mended cells could make a functioning hemoglobin molecule, which carries oxygen in normal red blood cells, and then successfully transplanted the stem cells into mice. The researchers say the study represents a proof of concept for the repair of blood-borne genetic diseases, such as sickle cell disease and thalassemia.

A paper describing the findings will be published online today in *Nature*. Postdoctoral scholars Daniel Dever, PhD, and Rasmus Bak, PhD, are the lead authors; Matthew Porteus, MD, PhD, associate professor of pediatrics, is the senior author.

A painful and deadly condition

Sickle cell disease affects 70,000 to 100,000 Americans and millions globally, inflicting suffering and high health-care costs. Children born in high-income countries typically survive with the chronic disease, while those born in low-income countries typically die before the age of 5. The disease results from a single mutation in the gene that codes for one of the protein chains that make up the hemoglobin molecule. Hemoglobin is the main constituent of red blood cells and allows the cells to pick up oxygen from the lungs and drop it off in tissues throughout the body, from the brain to the muscles.

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Sickle cells are rigid and sticky. They can clog blood vessels, causing pain and damaging organs.

The sickle mutation causes the red blood cells to make an altered version of the hemoglobin that forces the red cell into a sickle shape when oxygen levels drop. The sickle cells are rigid and sticky. They can clog blood vessels, causing pain and organ damage. In addition, sickle cells die faster than normal red blood cells, often leading to anemia, which can also damage organs.

The holy grail

Gene therapy, generally, has been the holy grail of gene-based therapeutics since the 1980s, with just a sprinkling of individual successes over the years. Increasingly, though, better techniques are raising hopes for practical therapies that can permanently cure genetic diseases like sickle cell.

"What we've finally shown is that we can do it," said Porteus. "It's not just on the chalkboard. We can take stem cells from a patient and correct the mutation and show that those stem cells turn into red blood cells that no longer make sickled hemoglobin."

Porteus said that in previous work, he has targeted sickle cell genes with an older gene-editing technology but that the new CRISPR technology is faster and easier to work with. "We spent half a dozen years trying to target the beta globin gene using the old technology," he noted, adding that within one week of trying CRISPR, they had an editing tool that worked much better.

CRISPR is a combination of an enzyme that can cut a selected DNA sequence and a "guide RNA" that takes the enzyme exactly where you want to make the cut — in this case, at the sickle cell mutation. Once the mutated DNA sequence has been removed, other tools can help paste in a copy of the normal sequence.

The Porteus team started with human stem cells from the blood of patients with sickle cell disease, corrected the gene mutation using CRISPR and then concentrated the human stem cells so that 90 percent carried the corrected sickle cell gene. The stem cells are a particular type, called hematopoietic stem cells, that make blood cells. The team injected the concentrated, corrected hematopoietic stem cells into young mice.

"These stem cells have a property to be able to get from the blood system into the bone marrow where they then set up shop and start making other blood cells," said Porteus. When the team examined the bone marrow of the mice after 16 weeks, the corrected stem cells were thriving there.

The corrected red blood cells needn't replace all of a patient's original sickle cells, said Porteus. If the proportion of sickle cells is below 30 percent, patients have no symptoms of disease. And corrected cells have about a tenfold advantage over uncorrected cells, he said. That's because red blood cells afflicted with sickle cell tend to sickle and die after an average of only 10 days. In contrast, the corrected cells

See SICKLE, page 6

Researchers explore how physicians can handle discrimination by patients

By Yasemin Saplakoglu

Researchers at the School of Medicine have identified strategies that doctors can use when facing discrimination from patients or their families.

"We think so much about doctors mistreating trainees, and we also talk about clinicians mistreating patients and discrimination in that direction," said Emily Whitgob, MD, a fellow in developmental-behavioral pediatrics at Stanford. "But we don't talk about it in this direction, and it happens."

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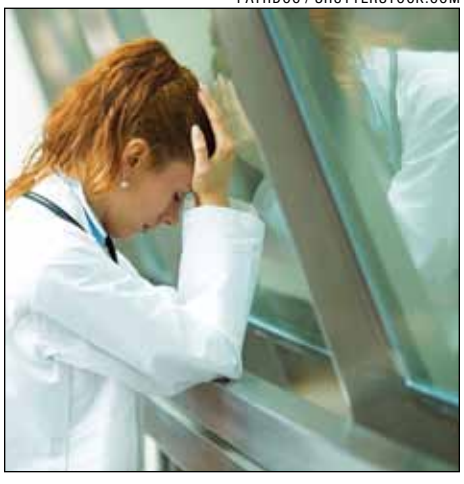

Indeed, a 2015 survey of Stanford pediatric residents revealed that 15 percent had experienced or witnessed medical trainees being mistreated by patients or their families.

A paper describing the strategies for dealing with discrimination was published online Oct. 26 in *Academic Medicine*. Whitgob is the lead author, and Alyssa Bogetz, the educational program developer for Stanford's pediatrics residency program, is the senior author. Program director Rebecca Blankenburg, MD, is a co-author.

Galvanized by personal experience

Whitgob said a personal experience with discrimination spurred her to initiate the study. "An intern I was supervising came to me very disturbed one day: Her patient asked if she was Jewish — because he didn't want a Jewish doctor," Whitgob said. "My intern isn't Jewish, but I am."

See DISCRIMINATION, page 7

Gene therapy for blistering skin disease appears to enhance healing in phase-1 clinical trial

By Krista Conger

Grafting sheets of a patient's genetically corrected skin onto open wounds caused by the blistering skin disease epidermolysis bullosa appears to be well-tolerated and improves wound healing, according to a phase-1 clinical trial conducted by researchers at the School of Medicine.

The results mark the first time that skin-based gene therapy has been demonstrated to be safe and effective in patients.

The findings were published Nov. 1 in *JAMA*. Associate professors of dermatology Peter Marinkovich, MD, and Jean Tang, MD, PhD, share senior authorship of the study. Senior scientist Zurab Siprashvili, PhD, is the lead author.

For the study, four adult patients with recessive dystrophic epidermolysis bullosa, an excruciatingly painful genetic skin disease, received the skin grafts.

MAX AGUILERA-HELLWEG

Paul Martinez, a participant in the clinical trial, displays an experimental skin graft on his left hand.

"Our phase-1 trial shows the treatment appears safe, and we were fortunate to see some good clinical outcomes," said Tang. "In some

See SKIN, page 6

More than 15 million children in high-mortality hotspots in sub-Saharan Africa

By Beth Duff-Brown

Stanford researchers have determined that more than 15 million children are living in high-mortality hotspots across 28 sub-Saharan African countries, where death rates remain stubbornly high despite progress elsewhere within those countries.

The study, which was published online Oct. 25 in *The Lancet Global Health*, is the first to record and analyze local-level mortality variations across a large swath of sub-Saharan Africa.

These hotspots may remain hidden even as many countries are on track to achieve one of the U.N. Sustainable Development Goals: reducing the mortality rate of children under the age of 5 to 25 per 1,000 by 2030. National averages are typically used for tracking child mortality trends, allowing left-behind regions within countries to remain out of sight — until now.

The senior author of the study is Eran Bendavid, MD, MS, an assistant professor of medicine and a core faculty member at Stanford Health Policy. The lead author is Marshall Burke, PhD, an assistant professor of Earth system science and a fellow at the Freeman Spogli Institute's Center on Food Security and the Environment.

SANDIS SVEICERS / SHUTTERSTOCK.COM

Stanford researchers developed a map that tracks the mortality rates of children under the age of 5 in sub-Saharan Africa. The map shows great variability of the rates within some countries — regions previously not singled out.

Decline in under-5 mortality rate

The authors note that the ongoing decline in under-5 mortality worldwide ranks among the most significant public and population health successes of the past 30 years. Deaths of children in that age group have fallen from nearly 13 million a year in 1990 to fewer than 6 million a year in 2015, even as the world's under-5 population grew by nearly 100 million children, according to the Institute for Health Metrics and Evaluation.

"However, the amount of variability underlying this broad global progress is substantial," the authors wrote.

"Mortality numbers are typically tracked at the national level, with the assumption that national differences between countries, such as government spending on health, are what determine progress against mortality," Bendavid said. "The goal of our work was to understand whether national-level mortality statistics were hiding important variation at the more local level, and then to use this information to shed light on broader mortality trends."

The authors used data from 82 U.S. Agency for International Development surveys in 28 sub-Saharan African countries, including information on the location and timing of 3.24 million births and 393,685 deaths of children under age 5, to develop high-resolution spatial maps of under-5 mortality from the 1980s through the 2000s.

Using this database, the authors found that local-level factors, such as climate and malaria exposure, were predictive of overall patterns, while national-level factors were relatively poor predictors of child mortality.

Temperature, malaria exposure, civil conflict

"We didn't see jumps in mortality at country borders, which is what you'd expect if national differences really determined mortality," said co-author Sam Heft-Neal, PhD, a postdoctoral scholar in Earth system science. "But we saw a strong relationship between local-level factors and mortality."

For example, he said, one standard deviation increase in temperature above the local average was related to a 16 percent higher child mortality rate. Local malaria exposure and recent civil conflict were also predictive of mortality.

The authors found that 23 percent of the children in their study countries live in mortality hotspots — places where mortality rates are not declining fast enough to meet the targets of the U.N. Sustainable Development Goals. The majority of these live in just two countries: Nigeria and the Democratic Republic of Congo. In only three countries do fewer than 5 percent of children live in hotspots: Benin, Namibia and Tanzania.

As part of the research, the authors have established a high-resolution mortality database with local-level mortality data spanning the last three decades to provide "new opportunities for a deeper understanding of the role that environmental, economic or political conditions play in shaping mortality outcomes." The database, available at http://fsedata.stanford.edu, is an open-source tool for health and environmental researchers, child-health experts and policymakers.

"Our hope is that the creation of a high-resolution mortality database will provide other researchers new opportunities for deeper understanding of the role that environmental, economic or political conditions play in shaping mortality outcomes," said Bendavid. "These data could also improve the targeting of aid to areas where it is most needed."

The research was supported by a grant from the Stanford Woods Institute for the Environment.

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

Microballoons could reveal how the small intestine adapts to dietary load

By Ula Chrobak

Our small intestine, among other organs, is malleable; it changes in size depending on how much we are eating. The question has been how the body regulates that growth.

Two Stanford Bio-X scientists, an engineer and a biologist, are using a balloonlike microdevice to answer that question in fruit flies. They hope to isolate factors that regulate changes in the small intestine's growth, with potential long-term impacts to human health research.

"Even as fully grown adult animals, our bodies are continually adapting. Understanding how a mature organ senses the need to grow is an important question in biology," said Lucy O'Brien, assistant professor of molecular and cellular physiology.

In both fruit flies and humans, eating stimulates intestinal cells to release a hormone closely related to insulin, which helps cells of the body take up sugar. This insulin relative activates stem cell division, enlarging the intestines so they can absorb more food. The intestines of a starved fly or human, conversely, will shrink. This process is reversible and repeatable, allowing organisms to adapt to changing environmental conditions. Maintaining a large gut when food is not available is energetically wasteful.

While the role of the insulin-like hormone in regulating intestine growth is understood, what causes its release is not. Prior research has not been able to distinguish whether the hormones are generated as a result of the physical force of intestine stretching or the sensing of nutrients.

To tease apart the causes, O'Brien has teamed up with Beth Pruitt, associate professor of mechanical engineering. The two received a Stanford Bio-X Interdisciplinary Initiatives Program seed grant for their project, "A gut feeling: Mechano- and chemo-sensory inputs controlling adaptive intestinal growth."

"Beth's superpower is developing microscale devices, the size of a single cell or chunk of tissue, that can deliver mechanical forces to tissue and look at the response," O'Brien said.

Lucy O'Brien

Beth Pruitt

Tiny balloons

O'Brien and Pruitt have proposed creating a "gut microballoon" to study adaptive gut responses in fruit flies. The microballoon, a tiny tubelike device, would be inserted into a chunk of fly gut floating in a media bath. Once inserted, the tube could be used to deliver nutrients or to blow up like a balloon, creating pressure inside the gut.

"In the universe of possibilities, the insulinlike signal gets turned on either from the sensing of nutrients or the mechanical forces of the gut getting stretched out," O'Brien said. "Using these tools from engineering, we can isolate potential causes and test each one."

The grant would help the researchers develop prototypes for the microballoon, which they could use in later studies of adaptive growth.

Simple genetics

By using fruit flies, O'Brien and Pruitt hope to first tackle the conceptual problem of understanding how adaptive organ responses work. This research could eventually be applied to humans.

"Fruit flies are awesome because their genome is so much simpler than in mammals. Mammals have many insulin receptors, but fruit flies only have one," O'Brien said.

This genome simplicity would allow the researchers to easily generate mutant flies. If the microballoon experiment suggests a particular nutrient is causing the intestines to release the insulin-like hormone, the scientists can follow up by producing mutant flies lacking the receptor for that nutrient. By seeing the response in mutant flies, the researchers can isolate individual receptors and determine what nutrient causes gut growth.

Ultimately, this research could be scaled up to applications in larger organisms and eventually humans. For example, the findings could be used to stimulate gut growth in order to help people with short bowel syndrome, whose abnormally short intestines limit their ability to absorb nutrients. The research might also be applied in the opposite direction: to slow intestine growth and limit calorie absorption in those with obesity.

Pruitt is a member of the Cardiovascular Institute, the Child Health Research Institute, Stanford ChEM-H and the Stanford Neurosciences Institute. ISM

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STANFORD MEDICINE

5 QUESTIONS

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

Bonnie Halpern-Felsher on teens and marijuana

There's a good news/bad news story playing out around teen smoking: After years of public health education about the dangers of cigarette use, teenagers' cigarette smoking is declining. But their marijuana use hasn't changed, with around 20 percent of 12th graders reporting that they recently smoked marijuana.

To find out why, Bonnie Halpern-Felsher, PhD, professor of adolescent medicine at the School of Medicine, and her team recently conducted a survey of 786 students from 10 large high schools across California. They asked the teens about their beliefs regarding marijuana and their patterns of use. Science writer Erin Digitale asked Halpern-Felsher to describe the highlights of the study, recently published online in Preventive Medicine.

1 You studied ninth and 12th graders' perceptions of the risks of using marijuana, tobacco and blunts, which are marijuana rolled in a tobacco leaf. What did you find?

HALPERN-FELSHER: Our study revealed a number of important findings about how adolescents think about marijuana and blunts. Adolescents in this study were more likely to use marijuana and blunts than cigarettes. Further, they believed that more than half of their friends were using marijuana. The majority of marijuana and blunt users reported getting these from their friends, used them most often with friends and at friends' houses, and often used marijuana or blunts when they were feeling stressed. Importantly, the adolescents who reported that their friends used marijuana were 27 percent more likely to use marijuana themselves. Compared with cigarettes, adolescents thought that marijuana and blunts were less likely to make them feel jittery or nervous, more likely to reduce stress and more likely to make them feel high or buzzed. Marijuana and blunts were also seen as less addictive, and perceived as easier to quit than cigarettes. Finally, more than half of the adolescents in the study reported seeing ads for the benefits of marijuana, and exposure to such ads was associated with a 6 percent greater chance of using marijuana.

2 Were you surprised by any aspect of your findings?

HALPERN-FELSHER: While we expected adolescents to report more friends using marijuana than cigarettes, we were surprised by how strong the peer influence was on where and how adolescents use marijuana. We were also surprised that stress was the No. 1 reason for use. It was also surprising that the adolescents believed that about half of their close friends were using marijuana, while national data show that the actual rates are somewhere from 16 to 25 percent. We also didn't realize how common it was for adolescents to see ads for the supposed benefits of marijuana, and how much such exposure to ads influenced their own use.

Bonnie Halpern-Felsher

We weren't surprised, but were concerned, that adolescents believe blunts are significantly less addictive than cigarettes. This was concerning because blunts contain nicotine, the drug that makes cigarettes and other tobacco products addictive.

3 You saw that teens perceive marijuana as less risky than tobacco. How does that perception line up with evidence from studies of the two substances' effects?

HALPERN-FELSHER: This is a complicated question, as much more research is needed. Some studies suggest that smoking marijuana has cardiovascular effects, including increased risk for heart attack. Studies also suggest that exposure to secondhand marijuana smoke impairs vascular endothelial function. Smoking a blunt confers additional risks, including nicotine addiction and cancer. More studies are needed to fully understand the effects of marijuana and blunts, but both products clearly entail significant risk.

4 How do you think adults — parents, health educators, teachers, etc. — might help correct the inaccuracies in teens' perceptions of marijuana?

HALPERN-FELSHER: Given that adolescents overestimated the extent to which their peers use marijuana, and that having friends who use marijuana was significantly related to the adolescents' own use, dispelling misperceptions about peer use might be effective. Studies have shown that changing perceptions that substance use is a normative behavior results in lower overall use. This approach can be employed by teachers, health educators, parents and health-care providers.

As our other research has shown, adolescents receive little education or information about marijuana and blunts. For instance, they don't understand that the tobacco leaves in which a blunt is rolled contain nicotine and many of the other harmful chemicals found in cigarettes. We need to explain to them that marijuana does confer risks, including likely risks to cardiovascular health and vascular function, and that marijuana is addictive, especially when used in the form of a blunt. We also need to explain that smoking any biomass can hurt your lungs.

Health messages also need to dispel the idea that marijuana is a way to reduce stress, and instead help adolescents find alternative stress-reducing strategies, such as exercise, healthy eating and so on.

5 In the upcoming election, California voters are being asked to decide on Proposition 64, which, if passed, would legalize recreational marijuana use for adults 21 and older. What aspects of your findings might help voters make a decision about how to vote on this proposition?

HALPERN-FELSHER: Any legislation regarding marijuana should include education and regulation to let youth know about the real and potential harms of marijuana. [If it passes, some of the tax revenue that would be generated by Proposition 64 would be earmarked for drug education, prevention and treatment programs for youth.] Simply legalizing marijuana without education and regulation will likely increase social normalization of marijuana, leading youth to feel that marijuana is OK to use. Indeed, our findings that adolescents think marijuana use is socially acceptable and that such perceptions are related to use suggests that legalizing marijuana will only increase such perceptions. In addition to comprehensive marijuana education within the schools, parents and educators need to be better-informed so that they can talk to young people, and health-care providers need to assess and discuss marijuana use with their adolescent patients.

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Also, voters may be interested to know that the American Academy of Pediatrics released a policy statement last year that favored decriminalizing marijuana possession but opposed legalizing recreational use. The AAP position, written by my Stanford colleague Seth Ammerman, MD, cited evidence that early marijuana use is associated with greater risk of addiction and greater potential harm to brain function. The AAP also expressed concerns that legalization would increase both teens' access to marijuana and their exposure to marijuana marketing.

Proposition 64 prohibits advertising marijuana directly to minors, but even with that caveat, teens will almost certainly see more marijuana advertising if the measure should pass. The connection we found between seeing marijuana ads and increased use lines up with the AAP's concern. ISM

Institute for Immunity, Transplantation and Infection awards grants

The Stanford Institute for Immunity, Transplantation and Infection has awarded seed grants to 15 interdisciplinary research projects led by faculty members and young investigators.

The following faculty teams and individuals each received $50,000 to fund their projects:

Eric Appel, PhD, assistant professor of materials science and engineering, and **Mark Davis**, PhD, professor of microbiology and immunology, for "Development of single-injection vaccines by leveraging biomaterial technologies."

Eugene Butcher, MD, professor of pathology, and **Juliana Idoyaga**, PhD, assistant professor of microbiology and immunology, for "Branching developmental pathways through high-dimensional single-cell analysis in trajectory space: Application to tissue-tropic dendritic cell development and the blood endothelial response to immunization."

Shirat Einav, MD, assistant professor of infectious diseases and of microbiology and immunology, **Stephen Quake**, PhD, professor of bioengineering, and **Purvesh Khatri**, PhD, assistant professor of biomedical informatics research and of biomedical data science, for "Identification of patients at risk of developing severe dengue infection."

Stephen Galli, PhD, professor of pathology, for "Detection and quantification of basophil activation during allergic reactions using a new avidin-based diagnostic tool."

Desiree Labeaud, MD, MS, associate professor of pediatric infectious diseases, **Holden Maecker**, PhD, associate professor of microbiology and immunology, and **Scott Boyd**, MD, assistant professor of pathology, for "Characterizing the effects of antenatal parasitic infection on fetal immune system development."

Matthew Lungren, MD, MPH, assistant professor of pediatric radiology, and **Christopher Contag**, PhD, professor of pediatrics and of microbiology and immunology, for "In-vivo imaging of phage therapy kinetics in eradication of biofilm-associated *Pseudomonas aeruginosa* lung infection."

Emmanuel Mignot, MD, PhD, professor of psychiatry and behavioral sciences, for "Genetics of T-cell response to trivalent flu vaccination and relevance to narcolepsy."

Grants for young investigators

The following young investigators each received $25,000 to fund their projects:

Sijuan Ding, PhD, postdoctoral research fellow in gastroenterology, for "Genetic interrogation of host factors essential to rotavirus infection."

Eliver Ghosn, PhD, instructor of genetics, for "Regenerative potential of human fetal versus adult HSC transplantation: B lymphocytes and macrophages heterogeneity."

Hedwich Kuipers, PhD, basic life research scientist in infectious diseases, for "Heparin sulfate-IL-2 interactions in the control of autoimmunity."

Marc Lucia Perez, PhD, postdoctoral scholar in surgery, for "Defining the CD8+ T-cell receptor and functional profile in T-cell-mediated allograft rejection."

Vamsee Mallajosyula, PhD, postdoctoral scholar at the institute, for "Delineating how the CD4+ T-cell response to influenza vaccination in humans relates to the antibody response."

Brook Ann Napier, PhD, postdoctoral scholar in microbiology and immunology, for "Determining the diagnostic and therapeutic power of complement-receptor C3aR in human sepsis."

Nicole Paulk, PhD, instructor of pediatrics, for "Sexually dimorphic viral-host interactions in pediatric liver diseases."

Heshan Peiris, PhD, postdoctoral scholar in developmental biology, for "Targeted immunosuppression and delivery of therapeutics to human pancreatic islets with chimeric antigen receptor T regulatory cells."

Funding for the projects comes from the Marion Avery Family Seed Grant Endowment for the institute, the institute's General Gift Fund, the School of Medicine Dean's Office and the Stanford Child Health Research Institute. ISM

Scientists discover hormone that controls maturation of fat cells

By Erin Digitale

Scientists at the School of Medicine have discovered a hormone that controls the first step in the maturation of fat cells. Its actions help explain how high-fat diets, stress and certain steroid medications cause obesity.

Brian Feldman

The new findings were published Oct. 25 in *Science Signaling*.

Around the body, fat depots contain many mature fat cells and small numbers of stem cells. These stem cells can differentiate into more fat cells, but until now, no one has known how the process was triggered.

The new research shows that mature fat cells make a hormone called Adamts1 that toggles the switch controlling whether nearby stem cells differentiate and prepare to store fat. High-fat diets and glucocorticoid medications change Adamts1 production, telling nearby stem cells to begin maturing, the research found.

"Intuitively, people understand that when you eat more, you get fatter," said Brian Feldman, MD, PhD, assistant professor of pediatrics and the study's senior author. "You're ingesting food, and some signal has to tell your body to make more fat. We didn't know what was gating or triggering that process *in vivo*. This new research goes a long way to fill in the in-between steps."

The paper's lead author is postdoctoral scholar Janica Wong, PhD.

In recent decades, scientists around the world have debunked the idea that fat cells are passive bags of calories. In addition to their storage function, mature fat cells are now known to send and receive many hormonal signals that help regulate metabolism.

Experiment with fat cells

To identify the role of Adamts1 and understand how it works, Feldman's team conducted a series of experiments using fat cells and their precursors in a dish, followed by studies in mice and humans. They started their search by looking for genes that change activity in response to glucocorticoid medications. These medications, which include prednisone and dexamethasone, have the serious, negative side effects of promoting obesity and diabetes. The scientists wanted to understand how. Among their findings:

Experiments using fat tissue from mice showed that mature fat cells normally make and secrete Adamts1. Its levels drop when mice are given glucocorticoids.

Mice that are genetically engineered to make more Adamts1 than normal have smaller-than-normal fat depots, and fewer mature fat cells.

When purified Adamts1 is added to fat stem cells in a dish, it can block glucocorticoid-induced differentiation, suggesting that it normally acts as an extracellular signal.

Once it reaches the fat stem cell, Adamts1 transmits its message through a set of intracellular signals that overlap with the cells' glucocorticoid response pathway. A cell-signaling molecule called pleiotrophin plays an important role in the pathway; blocking the molecule's signal blocks the stem cell's entire response to Adamts1.

Finally, after gathering this evidence that Adamts1 is a hormone, and that it plays a big role in controlling whether fat stem cells differentiate, the researchers fed high-fat diets to mice and humans and examined how this affected the Adamts1 signal. As expected, mice became fatter after eating a high-fat diet, with new fat cells maturing mostly in the animals' visceral fat tissue, the fat located around internal organs. The mice had decreased Adamts1 in this type of fat tissue. In subcutaneous fat tissue, the fat under the skin, the opposite response was seen: there was more Adamts1 production and less fat cell maturation.

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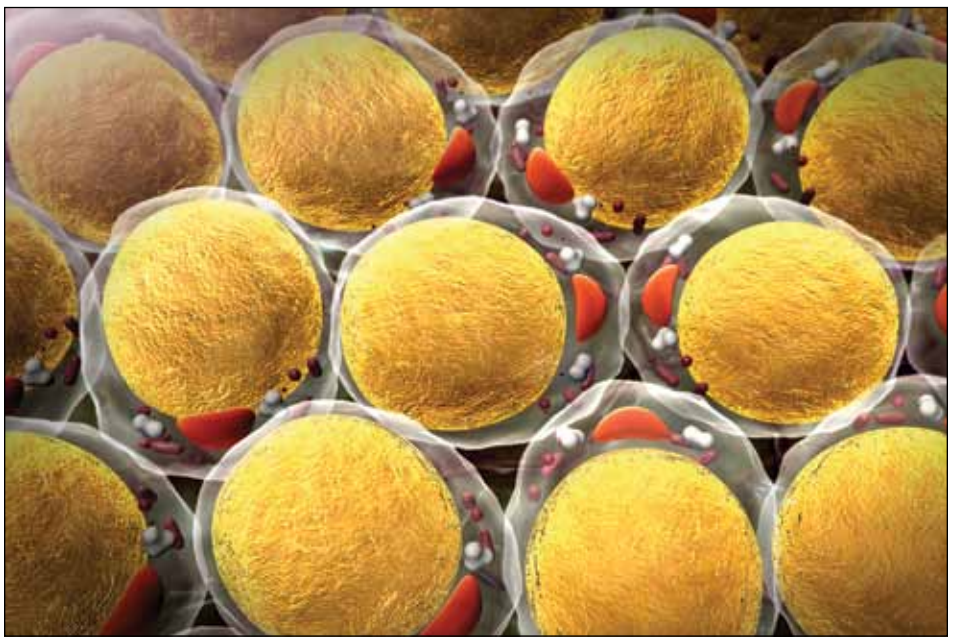

Researchers conducted a series of experiments that led to the discovery of a hormone that they believe triggers the production of more fat cells in the body.

These findings are consistent with earlier research showing that more visceral, but not more subcutaneous, fat cells mature when someone eats a high-fat diet, and suggest that Adamts1 is a major regulator of this difference between the two types of fat. In humans who gained weight while eating a high-fat diet, the research team saw that the Adamts1 responses were consistent with what was seen in mice.

"We do think there are going to be opportunities for new treatments based on our discoveries."

The effect of stress hormones

The results suggest how both high-fat diets and synthetic and natural stress hormones are tied to greater obesity. In essence, stress hormones send a message via Adamts1 to make more fat cells mature. "We think it is a signal that there may be hard times ahead, a trigger to store as much available energy as you can," Feldman said.

And the same set of signals works when people eat a high-fat diet but are not stressed or taking glucocorticoid medications, he added. "We've basically seen that the glucocorticoid signal is embedded in the high-fat feeding pathway. Connecting those dots together was really exciting."

The study's results do not exclude the possibility that other, undiscovered hormones also influence fat cells' decision to mature; however, Adamts1 is probably one of the most important, Feldman said. "There may be a group of regulators, but the potency of Adamts1 suggests it's a dominant signal, a major player," he said.

The scientists still have many ques-

See FELDMAN, page 8

City honors medical student for helping to save man's life

By Yasemin Saplakoglu

A few months ago, as Laura Lu rummaged through her childhood things, she came across a note her 8-year-old self had written in large block letters: "When I grow up I want to be a heart docter [sic]."

On Oct. 17, that same girl, now a third-year medical student at Stanford, was recognized by the city of Palo Alto for performing lifesaving CPR.

The health emergency that led to this honor occurred last spring.

Lu had only her upcoming board examinations in mind when she stepped into a printing and shipping store in Palo Alto on April 22 to drop off a textbook she wanted to get rebound. She returned for pickup a few hours later and heard some commotion behind the counter. When one of the managers of the store yelled, "Does anyone know CPR?" she dropped her backpack and rushed over. She found an employee, a man in his 40s, collapsed on the ground, without a pulse and not breathing. Quickly, she began performing the resuscitation technique.

The employee had suffered a sudden cardiac arrest — a condition in which the heart abruptly stops beating and blood stops flowing to the brain and other organs. If not treated within a few minutes, the condition often results in death.

'Completely fine a few hours earlier'

"I remember seeing him when I dropped off my book in the morning," Lu said. "That was part of the shock; he was completely fine a few hours earlier, and suddenly he was pulseless and not breathing."

She continued to perform CPR, taking turns doing chest compressions with a bystander who also rushed over to help. Lu guided the other woman through the steps of CPR. "I wish I had caught her name so that she could also be recognized for her contributions," Lu said.

PALO ALTO FIRE DEPARTMENT

Palo Alto Fire Chief Eric Nickel (left) and Police Chief Dennis Burns with Laura Lu, a medical student who was recognized by the city for helping to save the life of a man suffering a cardiac arrest.

Soon after, paramedics with the Palo Alto Fire Department arrived and took over. They defibrillated the patient a few times, gave him cardiac medications and attempted to open up his airway.

A fire department captain, Jesse Aguilar, was among members of the rescue team. "When I walked in, I could tell that Laura was well-trained," he said. According to him, Lu needed no instructions from the dispatcher on how to perform CPR. "Without her there at that time, I don't believe the victim would have survived, because as the studies show, early, aggressive CPR is what saves lives," he added.

By the time the paramedics brought the patient to Stanford Hospital, his pulse had returned. And a few days later, he walked out of the hospital with no permanent deficits from the incident, according to Palo Alto Fire Chief Eric Nickel.

But Lu didn't know that. "I was nervous, and I wasn't sure if he had survived," Lu said. "The adrenaline rush of not knowing is so hard to describe. I was sad and confused at the same time."

A few months later, she received a call from the Palo Alto Fire Department. Nickel told her that the man had survived and was back at work. They wanted to recognize her at the next city council meeting. "I was flabbergasted," Lu said.

"The person's greatest chance of survival is that citizen bystander CPR," Nickel said. "As a fire chief, it's great to know that we have this amazing community with a lot of extra rescuers out there, not just the ones that show up in the fire engine and ambulance."

Lu said that it was the first time she performed CPR on a person. Previously, she had only trained on mannequins. "This experience reminded me how important the information that we learn in class can actually be because you never know when something like this will happen and how you can be of help," she said.

Lu is currently a Howard Hughes Medical Institute Research Fellow and conducting research in bone fracture healing.

"We just want to congratulate her," Aguilar said. "Her efforts made all the difference." ISM

DNA-damage response links short telomeres, heart disorder

By Krista Conger

Progressively shortening telomeres — the protective caps on the end of chromosomes — may be responsible for the weakened, enlarged hearts that kill many sufferers of Duchenne muscular dystrophy, according to a study by researchers at the School of Medicine.

The researchers found that the shortening occurred specifically in the heart muscle cells, or cardiomyocytes, of laboratory mice bred to model the disease. The shortening triggered a DNA damage response that compromised the function of the cells' energy generators, or mitochondria. As a result, the cardiomyocytes were unable to efficiently pump blood throughout the body.

The new study is an extension of a 2010 study published in *Cell* and a 2013 study published in *Nature Cell Biology* by the same researchers. It identifies possible new therapeutic approaches for Duchenne muscular dystrophy and is the first to connect the molecular dots between previously disparate observations in affected cells.

"This is the first time that telomere shortening has been directly linked to mitochondrial function via a DNA damage response in a nondividing cell," said Helen Blau, PhD, professor of microbiology and immunology. "We've outlined the molecular steps in this process that lead to death, giving novel insights into the condition and identifying alternative strategies for heading off heart failure in human patients with Duchenne."

The researchers used a mouse model of the disease that they generated in 2013 that is the first to accurately recapitulate Duchenne muscular dystrophy in humans.

The ongoing shortening of the telomeres in cardiomyocytes is particularly surprising because the cells rarely divide. Telomeres naturally decrease in length with each cell division, acting as a kind of molecular clock counting down a cell's life span. Their length is normally stable in healthy tissues that don't divide.

"In mice, cell division in the heart normally stops within one week of birth," said Blau, who is also the Donald E. and Delia B. Baxter Foundation Professor and director of the Baxter Foundation Laboratory for Stem Cell Biology. "But we saw a proliferation-independent reduction in telomere length."

Blau is the senior author of the study, which was published online Oct. 31 in the *Proceedings of the National Academies of Science*. Postdoctoral scholar Alex Chang, PhD, is the lead author.

Difficult condition to study

Duchenne muscular dystrophy is the most prevalent form of the heritable muscular dystrophies. It is caused by mutations in the dystrophin gene that inhibit the production of the dystrophin protein, which connects the interior cytoskeleton of the muscle cell to the outside matrix. But until recently, it's been difficult to study because mice with the same dystrophin mutation didn't display the same symptoms as humans.

In the 2013 study, researchers in the Blau lab found that the reason humans suffer more serious symptoms than do mice is because of differences in the average lengths of their telomeres: Mice have telomeres about 40 kilobases in length, while human telomeres range from around 5 to 15 kilobases. When the investigators introduced a second mutation in the mice that reduced telomere length to more closely match that of humans, the "humanized" animals began to display the typical symptoms of the disease, including progressive muscle weakness, enlarged hearts and significantly shortened life spans.

Helen Blau

In particular, the researchers also observed that cardiomyocyte telomeres were significantly shorter than those in other muscle cells in the heart, such as the smooth muscle cells of the vasculature that do not require dystrophin for function. This was true not only in mice with mutated dystrophin, but also in four people with Duchenne muscular dystrophy who had recently died of cardiomyopathy. This was surprising because, although telomeres naturally shorten a bit with each round of cell division, their length is known to remain stable in non-dividing cells like cardiomyocytes.

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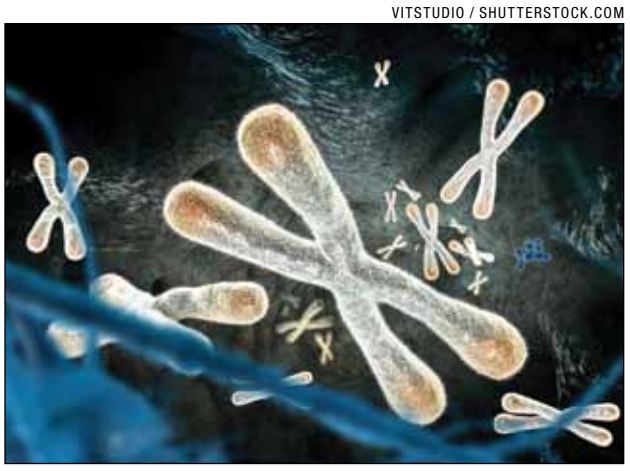


Telomeres are the protective caps on the ends of chromosomes. A new study shows that the progressive shortening of telomeres may be linked to enlarged hearts in those who have a type of muscular dystrophy.

"We knew from our previous study that telomeres play a role in the development of cardiomyopathy in Duchenne muscular dystrophy, but we didn't know the kinetics," said Chang. "Does this shortening occur suddenly, or gradually? Could it be possible to intervene? How exactly does it affect heart function?"

Telomere shortening, no cell division

Chang investigated telomere length in the cardiomyocytes of mice lacking the dystrophin protein at one, four, eight and 32 weeks after birth. He found that, although the cells stopped dividing within one week, the telomeres continued to shorten, losing nearly 40 percent of their length by 32 weeks.

A closer investigation of the affected mouse cardiomyocytes indicated that telomere shortening correlated with increasing levels of a protein called p53 that is known to be elevated in the presence of DNA damage. P53 in turn inhibits the expression of two proteins necessary for mitochondrial replication and function.

"The decrease in the levels of these mitochondrial master regulators led to a reduction in the number of mitochondria in the cell and mitochondrial dysfunction," said Blau. "They make less of the energy molecule ATP and have higher levels of damaging reactive oxygen species. This is what leads to the cardiomyopathy that eventually kills the mice."

Treating 4-week-old mice with a mitochondrial-specific antioxidant limited subsequent mitochondrial damage, the researchers found.

Chang and Blau are interested in learning exactly how the absence of functional dystrophin contributes to telomere shortening in cardiomyocytes. They are also planning to investigate whether artificially lengthening the telomeres could head off heart damage in the mice.

"More research is clearly needed before we attempt to devise any new therapies for humans," said Blau. "But these findings highlight the important role telomeres play in this and possibly many other human diseases in nondividing tissues like neurons and heart muscle."

Other Stanford co-authors of the paper are postdoctoral scholars Sang-Ging Ong, PhD, and Edward LaGory, PhD; Blau lab manager Peggy Kraft; professor of radiation oncology Amato Giaccia, PhD; and professor of cardiology Joseph Wu, MD, PhD.

The research was supported by the Baxter Foundation, the California Institute for Regenerative Medicine, the National Institutes of Health, a Stanford School of Medicine Dean's Fellowship, the Canadian Institutes of Health Research and the American Heart Association.

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

Stanford vs. Cal: There will be blood

By Sara Wykes

More than football will be at stake during Big Game Week.

Four days before the Nov. 19 kickoff of the 120th annual gridiron competition between Stanford and Cal, faculty, staff and students affiliated with the two universities will participate in a one-day contest to see who can donate the most blood. The Rivals for Life competition, now in its 11th year, is scored just like the football game: Points or pints — the most wins.

The contest winner earns bragging rights — and Stanford has won the drive nine times — but the donated blood is the true goal. Typically, each university has donated more than 200 pints during the contest. Blood donations, in such forms as whole blood, red cells, plasma and platelets, sustain demand that is never-ending, sometimes unpredictable and modulated by strict regulatory controls for temperature and testing. In 2015, almost 6,000 patients at Stanford Health Care and Stanford Children's Health received 73,000 transfusions of blood products.

NORBERT VON DER GROEBEN

Concepcion Batilo, a lab technician, works at the Stanford Blood Center in Palo Alto.

'You can't just give any blood to any person'

"If you look at the total number of blood units you collect and those who receive it, you would think there's never a shortage," said Tho Pham, MD, associate medical director of the Stanford Blood Center. "But you can't just give any blood to any person" because of blood-type incompatibilities.

So the blood center holds continuing blood drives, on campus and throughout the Peninsula and South Bay, to collect its annual goal of 54,000 pints. Less than 10 percent of the general population donates blood, although almost 40 percent is eligible. Some people are permanently excluded from donating blood for medical reasons, including a history of certain blood cancers. Others must wait temporarily after travel to a region where malaria is active or until certain medications, like blood thinners, are no longer active in the blood. The center has a remarkable group of regular donors, said donor recruitment manager Karen Hendryk. More than 50 people have given 100 pints. Several donors are in the 200- to 400-pint category, and three people have given at least 500 pints.

Limited lifetime

Once collected, the blood is handled as carefully as its temperature sensitivity dictates. Blood must be stored at temperatures between 33.8 and 42.8 degrees F — not too far from a home refrigerator's recommended setting. Even at those cool temperatures, blood has a limited lifetime of 28 to 42 days.

NORBERT VON DER GROEBEN

Stanford students participate in the 2015 Rivals for Life. On Nov. 15, the annual blood drive will again pit Stanford against Cal in the contest to see which university can donate the most blood in a day.

The blood center stays in close contact with Stanford Health Care's Transfusion Medicine Service, which is the central hub for distributing the donated blood products where they're needed — most frequently, for surgeries or trauma care. While it's not possible to predict precise needs, Pham said, "We take a snapshot daily of blood products and try to match that with what we're collecting. Our responsibility is to be good stewards of our blood supply."

The Transfusion Medicine Service also strives to ensure the most effective use of blood products, said its director, Hua Shan, MD, a professor of pathology. In the past few years, SHC has added features to Epic, its electronic medical record **See BLOOD, page 8**

Skin

continued from page 1

cases, wounds that had not healed for five years were successfully healed with the gene therapy. This is a huge improvement in the quality of life for these people."

People with epidermolysis bullosa lack the ability to properly produce a protein called type-7 collagen that is needed to anchor the upper and lower layers of the skin together. As a result, the layers slide across one another upon the slightest friction, creating blisters and large open wounds.

The most severe cases are fatal in infancy. Other patients with recessive dystrophic EB can live into their teens or early adulthood with supportive care. Often these patients die from squamous cell carcinoma that develops as a result of constant inflammation in response to ongoing wounding.

The Stanford researchers showed that it was possible to restore functional type-7 collagen protein expression in patient skin grafts to stop blistering and allow wounds to heal. They also found that the protein continued to be expressed and that wound healing was improved during a year of follow up.

Looking to build upon results

The researchers seek to build upon these promising early results in a new trial that will include patients ages 13 and older.

"Moving into the pediatric population may allow us to intervene before serious chronic wounds and scars appear," said Marinkovich, who directs the Stanford Blistering Disease Clinic. Repeated rounds of wounding and scarring on the fingers and palms, for example, often lead to fusion of the skin and the formation of what's known as a "mitten hand."

Siprashvili used a virus to deliver a corrected version of the type-7 collagen gene into batches of each patient's skin cells that had been harvested and grown in the laboratory. He coaxed these genetically corrected cells to form sheets of skin about the size of an iPhone 5. The sheets were then surgically grafted onto the patient's chronic or new wounds in six locations.

The researchers tracked the status of the grafts at one-, three- and six-month intervals for at least a year, checking to see if they stayed in place and caused wound closure. They also looked for any evidence of an immune reaction to the grafts, and whether the grafts continued to make the corrected type-7 collagen protein.

All 24 grafts were well-tolerated, the researchers found. Furthermore, they could detect expression of the type-7 collagen protein in the correct location of the skin in nine out of 10 tissue biopsies at three months. After 12 months, they were able to detect the collagen protein in five out of 12 biopsies.

Peter Marinkovich

Wound healing

Similar results were seen with wound healing. After three months, 21 of the 24 grafts were intact. This number dropped to 12 out of 24 after one year.

"Even a small improvement in wound healing is a huge benefit to the overall health of these patients," said Tang. "For example, it may reduce the likelihood of developing squamous cell carcinoma that often kills these patients in young adulthood."

Coupling grafts with hand surgery to break up scarred, fused tissue could help patients maintain the use of their hands, Marinkovich said.

> "Even a small improvement in wound healing is a huge benefit to the overall health of these patients."

Tang, Marinkovich and their colleagues will continue to monitor the patients in the phase-1 trial throughout their lifetimes to assess any long-term effects of the grafts.

The completion of the phase-1 trial and the potential to improve upon these outcomes is due to a concerted, long-term effort at Stanford to find ways to help young patients with this devastating disease.

The researchers are now starting a phase-2 clinical trial and are looking for new patients. For more information, send an email to tangy@stanford.edu or mpm@stanford.edu.

"This trial represents the culmination of two decades of dedicated clinical and basic science research at Stanford that began with the arrival of the former dean of the School of Medicine, Eugene Bauer, who set up the multidisciplinary EB Center at Stanford," said Tang. "We have been working for a long time to get to this potential therapy into patients. We had to discover the genes and proteins involved and the responsible mutations. We then had to learn to deliver the corrected gene and grow those cells into sheets suitable for grafting."

"We could not have reached this point without the support of the EB patients and their families," said Marinkovich. "Since the time of my research training in the laboratory of Robert Burgeson, PhD, who discovered type-7 collagen, I've been deeply motivated to contribute to the EB community, and it is very satisfying to be able to finally see this molecular therapy come to fruition."

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

Other Stanford co-authors are research assistant Ngon Nguyen; former research associates Emily Gorell and Kylie Loutit; clinical assistant professor of dermatology Phuong Khuu, MD; clinical assistant professor of anesthesiology Louise Furukawa, MD; professor of surgery Peter Lorenz, MD; former instructor of dermatology Thomas Leung, MD, PhD; clinical associate professor of dermatology and of pathology Kerri Rieger, MD, PhD; professor of dermatology Paul Khavari, MD, PhD; and professor emeritus of dermatology and of pediatrics Alfred Lane, MD.

The research was supported by the National Institutes of Health, the Epidermolysis Bullosa Medical Research Foundation and the Epidermolysis Bullosa Research Partnership.

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

Sickle

continued from page 1

live the length of normal red blood cells, about 120 days. So the numbers of corrected cells rapidly outstrip those of uncorrected cells.

Is it safe?

Although gene therapy research has made great strides in recent years, it has yet to be widely deployed, and no CRISPR-edited genes have yet been tested for safety or efficacy in human clinical trials. Examples of potential problems include unforeseen immune reactions or altering the wrong sequence of DNA — so-called off-target effects. The effects of gene editing in general are impossible to predict.

LUCILE PACKARD FOUNDATION FOR CHILDREN'S HEALTH

Using the CRISPR gene-editing technique in stem cells, Matthew Porteus and his research team repaired the gene that causes sickle cell disease, and the mended stem cells were successfully transplanted into mice.

As Porteus said, "The consensus in the field is that there's no one test we can do to prove that something is safe. We can't just say, 'Oh, just run this test, and that'll show if it's safe or not.' That test doesn't exist." Instead, he said, a series of different tests may each offer some insights about potential safety. For now, Porteus and his team found that their corrected human hematopoietic stem cells seemed to behave like normal, healthy human hematopoietic stem cells.

"We're excited about working to eventually bring this type of therapy to patients," said Porteus. "Stanford is building the infrastructure so that we can take our discovery in the lab and develop it so we can scale up the laboratory process to a process that will be needed to treat a patient. We hope to develop the entire process here at Stanford."

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

Other Stanford co-authors are professor of pediatrics Kenneth Weinberg, MD; associate professor of medicine Ravindra Majeti, MD, PhD; assistant professor of pediatrics Anupama Narla, MD; postdoctoral scholars Andreas Reinisch, MD, PhD, Mara Pavel-Dinu, PhD, and Ayal Hendel, PhD; research associates Carmencita Nicolas and Alec Wilkens; research assistant Nivi Saxena; cord blood coordinator Sruthi Mantri; medical student Gabriel Washington; and undergraduate research assistant Joab Camarena.

This research was supported by the National Institutes of Health, the Stanford Child Health Research Initiative, the Laurie Kraus Lacob Scholar Award in Pediatric Translational Research and the Laurie Kraus Lacob Endowment Fund.

Stanford's Department of Medicine also supported the work.

Porteus has equity interest in CRISPR Tx, where he is scientific founder and a member of the advisory board. ISM

New virtual center launches for Indo-U.S. biomedical collaborations

By Jennie Dusheck

A virtual center for collaboration between biomedical researchers in India and the United States has won financial support from the nonprofit Indo-U.S. Science & Technology Forum.

The center is the brainchild of Sanjay Malhotra, PhD, associate professor of radiation oncology and of radiology at the School of Medicine, and his co-principal investigator, Kanury Rao, PhD, at the Translation Health Science and Technology Institute in India.

Sanjay Malhotra

One of just five proposals selected by the forum in 2015 for funding as an Indo-U.S. Knowledge R&D Networked Joint Center, the Center for Integrative Biology of Non-Communicable Diseases comes with a starter grant of $72,000 to fund international travel and housing.

Of the 56 million people who die globally every year, more than 65 percent die of noncommunicable diseases. These include cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. More than 90 percent of them are preventable.

The center will focus primarily on the biomolecular networks that link cancer, diabetes and cardiovascular diseases. A common denominator of all these diseases is thought to be metabolic syndrome, which, some evidence suggests, promotes the development of noncommunicable diseases generally. For example, said Malhotra, one clue is that patients taking the Type 2 diabetes drug metformin appear to have a reduced risk of developing breast cancer.

"We want to know, 'What are the common pathways that influence cancer, diabetes and heart disease?'" said Malhotra. "And how can we use that information to develop new therapies for these different yet somehow related diseases?"

The center can help researchers at Stanford find research partners in India with similar interests and complementary resources, he said.

Looking ahead, it's possible the center could help Stanford researchers gain access to databases of patient health information in India, he said. This access could open the doors to conducting studies that, for example, compare the epigenetic profiles of patients exposed to high levels of air pollution in cities to the profiles of matched relatives in rural villages. ISM

5 QUESTIONS

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

Peter Kim on the Biohub infectious disease project

Fighting infectious disease will be one focus of the recently announced Chan Zuckerberg Biohub, and Peter Kim, PhD, professor of biochemistry at Stanford, has been selected to lead the effort.

The Biohub, an independent research institute formed in partnership with Stanford, UC-San Francisco and UC-Berkeley, is being funded by the Chan Zuckerberg Initiative as part of its pledge of $3 billion toward scientific endeavors aimed at finding ways to cure, prevent or manage all diseases by the end of the century. Facebook founder Mark Zuckerberg and his wife, Priscilla Chan, MD, established the Chan Zuckerberg Initiative in 2015.

Stanford Report *recently asked Kim for this thoughts on the Biohub's infectious disease project and what he hopes to accomplish.*

1 The Chan Zuckerberg Initiative announced a big goal for its science investment. Do you think it's achievable?

KIM: The mission is, on the surface, completely outrageous. Cure, prevent or manage every disease by the end of the century? But in his presentation Mark made the point that all the advances we take for granted in medicine and the enormous increase in the average human lifespan have occurred in only 100 years. Then he says, "So what do you expect to happen by the end of the century?" This argument took me from incredulous to "I don't know, maybe it could happen."

The second point he made is that we spend 50 times more money treating disease than we do on finding ways to cure or prevent disease. If you are a company and you spent 50 times more dealing with problems than dealing with the future, that's a failure. That was pretty insightful. I give Mark and Priscilla a ton of credit for coming out with arguments that are unique and compelling.

2 Is there a particular focus to the work at the Biohub?

KIM: The Biohub is going to have a heavy technology, engineering and computer science focus, which makes a lot of sense for the Bay Area and avoids being duplicative with other initiatives. It will also be developing cutting-edge technologies that are applicable to the life sciences. Steve Quake [PhD, professor of bioengineering and applied physics at Stanford] and Joe DeRisi [PhD, professor of biochemistry and biophysics at UCSF], the co-leaders of the Biohub, are committed to ensuring that people at the three universities will have access to these technologies.

3 What are the two research projects being run out of the Biohub?

KIM: One is the cell atlas project, which has to do with identifying and characterizing all the different types of cells in the body. Using recently developed technologies, the project will not only characterize the cells, but identify the genes that are active in each cell type and manipulate the proteins to learn how the cells behave in health and disease states. Once it's done, the cell atlas will be a tool available to scientists worldwide.

The second project, which I'm leading, is on infectious disease. That project has four components: detect, respond, treat and prevent.

4 Can you explain what you hope to accomplish in those four areas?

Detect: With advances in next-generation sequencing it's possible to detect the genetic material of infectious agents in the blood and cerebrospinal fluid. Indeed, Joe and Steve have each already made major contributions in this regard. If that technology compares favorably with the standard methods of detection that involve culturing and waiting several days, it could significantly speed detection and identification of infectious agents. Certainly we're interested in making this technology better and more routine.

Peter Kim

We'll also be interested in developing new tools to detect infections, particularly in geographic areas where we don't normally have access to cutting-edge technology. For example, a problem in the recent Ebola outbreak was that you would have to ship a blood sample and wait many days to diagnose the infection, which often was too late.

Treat: We aren't a drug company and we won't be running clinical trials, but there are two general areas that we want to impact initially. First, we will work with the cell atlas project to better understand interactions between infectious agents and human cells and provide insights and validate potential drug targets that others would want to capitalize on.

Second, we will enhance technology to identify and isolate individual B cells producing neutralizing antibodies from people who have survived infections. What I would like is for us to be in a situation where if there is a new infectious disease outbreak, we can rapidly create antibodies that are potential therapeutics that we could hand off to a company or agency for scale-up.

Prevent: The most cost-effective way to prevent infectious disease is through vaccines. The focus is not going to be making vaccines per se, but developing new technologies for creating or enhancing vaccines. By focusing on improving vaccine technology we can have an impact beyond an individual disease.

Here I think there are a lot of possibilities. Bioengineers in particular are developing different methods including new nanoparticle-based vaccine technologies and nucleic acid-based technologies that we are interested in developing and testing. We also want to take advantage of advances that have occurred in nanotechnology and in computer-assisted protein design to create new approaches to develop vaccine candidates. We are also interested in using machine-learning strategies to interrogate clinical, laboratory and epidemiological data for insights into preventing disease with vaccines.

Respond: History shows that when outbreaks occur, society is slow to respond. We want to be positioned to be able to activate a team to respond rapidly to a disease outbreak to provide information and materials that will be helpful in fighting the outbreak.

It's not that we'll have people sitting around waiting to respond. The idea is we will have the expertise to respond rapidly by the nature of what we are doing when we aren't responding. We're going to have a community of investigators that are interacting with the infectious disease project so that when an outbreak occurs people can rapidly get together and contribute.

5 How does this project relate to work going on in your own lab?

KIM: My lab is working on creating vaccines for HIV and other viruses, in addition to a new interest in cancer immunotherapy. Both of these areas have to do with finding novel ways of treating or preventing disease. I also work in collaboration with other labs that are part of Stanford ChEM-H, which spans basic sciences, engineering and medicine to find solutions to human health challenges. These collaborations within Stanford are not unlike the engineering, science and medical collaborations we'll need to form across Bay Area universities to ensure success of the infectious disease project. It's similar to my own work but scaled up because we'll have primary investigators at the Biohub working on the project, as well as collaborators at all three universities. **ISM**

Discrimination

continued from page 1

When Whitgob brought up this story at a weekly meeting to a roomful of doctors in training, she was surprised by their reaction. "Half of the room was in tears" as they talked about the difficulties of facing discrimination from patients, she said. "They're women, people of color, different religions — and feeling very powerless."

Alyssa Bogetz

Emily Whitgob

The researchers recruited 13 physicians from Stanford's pediatric residency program evaluation committee, each with responsibilities for supporting and teaching doctors in training. "In the case of a discriminatory event, these people would be at the forefront," Whitgob said. "They are there for residents to go to, and they want to be there."

Bogetz conducted 75-minute interviews with these physicians on how they would advise their trainees to respond and how they would themselves respond to three scenarios of discrimination. One scenario involved racial discrimination, and the other two involved religious and gender discrimination.

When the researchers analyzed the responses, several themes emerged.

To validate or repudiate?

One was the importance of assessing illness acuity. In the case of an emergency, the participants agreed that doctors should ignore discriminatory remarks and focus on providing urgent medical care. "If this is a child who has a gunshot wound and is bleeding out, then none of the other approaches are appropriate because first you have to save this child," Whitgob said.

The participants also agreed that it is best for trainees to depersonalize the event. Rather than taking the discriminatory behavior personally, they recommended dismissing the remarks as the speaker's own problem.

Most, but not all, of the participants said that identifying, naming and validating the emotional experience underlying the discriminatory remarks was central to establishing trust with the families. They suggested that trainees "cultivate a therapeutic alliance" — in other words, build rapport with the patient's family to emphasize the importance of their child's health relative to all else, including their prejudice. This rapport may be established, these physicians asserted, through acknowledging the discriminatory remarks and exploring underlying reasons for them.

However, four of the physicians said it was best to simply focus on immediate medical needs and convey that discrimination of any sort is unacceptable. They believed that accommodating families' requests for alternative doctors would reinforce prejudicial thoughts and discriminatory behavior.

All of the participants expressed their hopes for ensuring a safe learning environment for trainees. While acknowledging the importance of discussing uncomfortable situations with colleagues and supervisors, they insisted that trainees should make their own decisions about how to deal with discrimination from patients or their families. They agreed that initial medical school training and faculty development could help to prepare for those situations.

"What's heartening in this study is that in a busy medical setting with a lot of demands, nobody really wants more trainings, but when we asked the participants if they would like to have more on this topic, everyone except for one person said absolutely," Whitgob said.

The next step

The next step is to create programs based on the study's findings to train both experienced and new medical staff to properly respond to discriminatory situations, Whitgob said. The participants recommended case-based discussions as one way to practice handling these scenarios.

"We recommend discussion of this type of mistreatment early in training so trainees feel equipped to respond and feel permission to remove themselves from care when necessary," the researchers wrote.

Whitgob hopes this study will first and foremost create a conversation. "These things will happen, and there's no way to prevent them," she said. "It's going to be shocking when someone says something horrendous, but previous training may help to have some kind of action plan in the back of your mind that you can employ." Advance preparation would give trainees time to ask questions such as, "What are my boundaries? What am I willing to hear? Where will I draw the line and say I'm not comfortable?"

Though this study was based on experiences at a pediatric hospital, the results are relevant to adult hospitals as well, and could provide a framework for training programs, the researchers said.

Stanford's Department of Pediatrics supported this work. **ISM**

James Chen appointed chair of chemical and systems biology

By Rosanne Spector

James Chen, PhD, has been appointed chair of the School of Medicine's Department of Chemical and Systems Biology. His five-year term began Sept. 1.

"My colleagues in the department were incredibly helpful and supportive when I joined Stanford as an assistant professor," said Chen, a professor of chemical and systems biology and of developmental biology, who came to Stanford in 2003.

"I look forward to sustaining that collegial and collaborative culture, while helping empower our faculty and students to pursue cutting-edge, innovative science," he added.

Chen succeeds Tobias Meyer, PhD, professor of chemical and systems biology and the Mrs. George A. Winzer Professor in Cell Biology, as chair of the department, which currently consists of 12 faculty, 50 graduate students and 45 postdoctoral researchers.

"Biomedical science is becoming increasingly molecular, quantitative and 'omic,' and our department uniquely integrates all three themes," said Chen. "Our faculty have also contributed to the broader School of Medicine community by founding the High-Throughput Bioscience Center, the Stanford Center for Systems Biology and SPARK. As we move forward, I would like to build upon that community spirit."

Lloyd Minor, MD, dean of the School of Medicine, praised Chen and Meyer in his email to the school's executive committee members: "A distinguished investigator and a trusted mentor, Dr. Chen is widely respected by colleagues for his commitment to Stanford and his vision for the future of chemical and systems biology. … Please join me in thanking Tobias for his thoughtful leadership and exceptional service and congratulating James on his new role."

James Chen

Native of Missouri

Born and raised in Rolla, Missouri, Chen considers the crayfish in the creek behind his childhood home as his first biology study subjects. He began his formal research training in Harvard's Department of Chemistry and Chemical Biology, pursuing research as an undergraduate with professor George Whitesides, PhD, and then completing his doctorate with professor Stuart Schreiber, PhD.

Chen went on to pursue postdoctoral studies in embryology at the Marine Biological Laboratory in Woods Hole and then at Johns Hopkins University with professor Philip Beachy, PhD, who is now on the Stanford faculty. During this time, Chen combined his interest in organic chemistry and embryonic patterning by investigating how a plant-derived chemical known as cyclopamine induces cyclopia — a rare birth defect characterized by a single eye. His discovery that cyclopamine inhibits the transmembrane protein Smoothened — a Hedgehog pathway component involved in tumor formation — led to the development of anticancer drugs that mimic cyclopamine action.

At Stanford, Chen has pioneered the application of chemical tools in complex biological systems, particularly those related to embryonic development and cancer. For example, his team has synthesized light-activatable molecules for controlling gene expression in zebrafish embryos. More recently, they have been working toward new ways to visualize gene expression in live organisms.

Outside of the laboratory, Chen's fascination with water-dwelling creatures remains strong. A lover of fly fishing, he's especially interested in trout. "Fly fishing and scientific research actually have a lot in common — mastering a highly technical discipline, overcoming failure through reasoning and persistence, and finding happiness in the process as much as the purpose. Similar lessons can be learned in the river and in the lab," he said. ISM

OF NOTE

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

JAMES LOCK, MD, PhD, professor of psychiatry and behavioral sciences, was awarded a grant of $100,000 from the National Eating Disorders Association to study avoidant/restrictive food intake disorder. His research focuses on the treatment of eating disorders in children and adolescents.

JULIA PALACIOS, PhD, was appointed assistant professor of biomedical data science and of statistics, effective Sept. 1. Her research uses statistical methods to infer evolutionary parameters from whole genomes.

LAURA SIMONS, PhD, was appointed associate professor of anesthesiology, perioperative and pain medicine, effective Sept. 1. She is a pediatric psychologist whose research and clinical work focuses on the influence of pain-related fear in children and adolescents with chronic pain.

SEDA TIERNEY, MD, assistant professor of pediatrics, has received a two-year, $100,000 grant from the Marfan Foundation to study the effects of exercise on children and adolescents with Marfan syndrome, a connective-tissue disorder. She will share the grant with a researcher from Midwestern University. Tierney is director of the Pediatric Vascular Research Laboratory and director of research at the Non-Invasive Imaging Laboratory, both at Lucile Packard Children's Hospital Stanford.

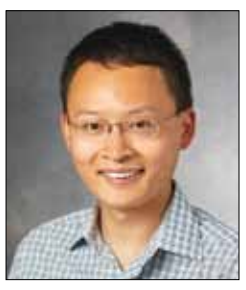
JAMES ZOU, PhD, was appointed assistant professor of biomedical data science, effective Sept. 1. His research uses machine-learning techniques to examine questions in human genomics. ISM

James Lock

Julia Palacios

Laura Simons

Seda Tierney



James Zou

Two faculty members named Bass Fellows

Two faculty members in the School of Medicine has been appointed or reappointed Bass University Fellows in Undergraduate Education.

Named in honor of Anne T. and Robert M. Bass, the fellows program recognizes faculty members, including those from the graduate and professional schools, for extraordinary contributions to undergraduate education.

Paul Fisher

Donna Bouley

Paul Fisher, MD, was appointed the Dunlevie Family University Fellow in Undergraduate Education. He is the chief of child neurology, the Bing Director of the Program in Human Biology, the Beirne Family Professor in Pediatric Neuro-Oncology and a professor of neurology and neurological sciences and of pediatrics. His research interests include the epidemiology of and treatments for pediatric brain tumors and the neurologic effects of cancer and cancer therapy. He teaches the undergraduate course "Cancer Epidemiology."

Donna Bouley, DVM, PhD, professor of comparative medicine, was reappointed the Kleinheinz Family University Fellow in Undergraduate Education. She founded and advises the Stanford Undergraduate Pre-Vet Club. She applies her skills in comparative pathology to advise many researchers who work with animal models on topics including the pathology of minimally invasive cancer treatments, the use of hypoxic cytotoxic drugs to treat cancer, host-pathogen interactions, phenotypic analysis of transgenic and knockout mice, and infectious diseases of frogs. She teaches the undergraduate course "Comparative Anatomy and Physiology of Mammals."

Each appointment is named in honor of donors who made significant gifts to the Stanford Fund for Undergraduate Education during the Campaign for Undergraduate Education, which ended in 2005. ISM

Feldman

continued from page 4

tions left to answer about Adamts1, including whether it might somehow be used as a target for anti-obesity drugs.

"That won't be a simple answer," Feldman said. "If you block fat formation, extra calories have to go somewhere in the body, and sending them somewhere else outside fat cells could be more detrimental to metabolism. We know from other researchers' work that liver and muscle are both bad places to store fat, for example. We do think there are going to be opportunities for new treatments based on our discoveries, but not by simply blocking fat formation alone."

The results could also help scientists understand how fat formation in childhood influences lifelong obesity risk, Feldman said. "We know that fat is a critical endocrine organ, formed almost exclusively during childhood," he said. "The rate of fat formation in childhood has lifelong implications, and understanding how that's controlled and regulated is very important."

Other Stanford co-authors of the paper are postdoctoral scholars Katherine Krueger, PhD, Abhishek Aggarwal, PhD, and Hongqing Du, PhD; research associate Maria José Costa, PhD; and Tracey McLaughlin, MD, associate professor of medicine.

Feldman is a member of Stanford's Child Health Research Institute and is the Bechtel Endowed Faculty Scholar in Pediatric Translational Medicine.

The research was funded by a National Institutes of Health Director's New Innovator Award, Stanford SPARK Translational Research Program, the Glenn Foundation for Medical Research, the NIH, a Stanford School of Medicine Dean's Postdoctoral Fellowship, the Lucile Packard Foundation for Children's Health and Stanford's Child Health Research Institute.

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

Blood

continued from page 5

system, to promote appropriate use of blood transfusion. "For a leading academic medical center providing comprehensive care to a complex patient population, improving the safety, effectiveness and appropriateness of blood transfusion is a critical component of the program for enhancing the quality of patient care overall at SHC," she said.

The latest safety measure that will soon be adopted by the Stanford Blood Center is a technology that can further reduce the risk of transfusion-transmitted infections. "I think people may not appreciate all the efforts and the challenge of delivering a safe bag of blood to the bedside," Shan said. "There are so many things that need to be done, starting with finding a safe donor."

The Rivals for Life drive takes place on Nov. 15. Although Stanford leads the series 9-1, last year's margin of victory was small: only 12 pints. To help the Cardinal run up the score, visit http://bloodcenter.stanford.edu/donate. ISM