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 modified 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.

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.

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.”

Indeed, a 2015 survey of Stanford pediatrics 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 Bogart, 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.”

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

“Our phase-1 trial shows the treatment appears safe, and we were fortunate to see some good clinical outcomes,” said Tang, “In some cases skin grafts on his left hand.

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 correct 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 Martinovich, MD, and Jean Tang, MD, PhD, share senior authorship of the study. Senior scientist Zurab Siprashvili, PhD, is the lead author.

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“Our phase-1 trial shows the treatment
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 unacceptably high despite progress elsewhere within those countries.

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

These hotspots may remain hidden even among many countries where data is available to achieve one of the U.N. Sustain- 
able Development Goals: reducing the mortality rate of children under the age of 5 to 2 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 Erin Bendavid, MD, MS, an assistant professor of medicine and a core faculty member at Stanford Health Policy. The lead author is Mariana Bendas, PhD, an assistant profes- sor of Earth system science and a fellow at the Free- man Spogli Institute’s Center on Food Security and the Environment.

**Decline in under-5 mortality rate**

The authors note that the ongoing decline in under-5 mortality rates across the world is significant and 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.

The authors found that local-level variations are typically tracked at the na- tional level, with the assumption that national differ- ences between countries, such as government spending on health, are what determine progress against mor- tality, Bendavid said. 

“ar 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 infor- mation to shed light on broader mortality trends.”

The authors used data from 82 U.S. Agency for International Develop- ment surveys in 28 sub- Saharan African countries, revealing 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 trends in the 1980s through the 2000s.

Using this database, the authors found that local-level factors, such as climate and malaria ex- posure, 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% 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 pro- vide “new opportunities for a 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.”

“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.

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**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 role of the insulin-like growth factor 1 receptor, or IGF-1R, is one example. When the hormone IGF1 binds to IGF-1R, it stimulates gut growth in order to help people with short bowel syndrome, whose abnormally short intestines limit their ability to absorb nutrients. The researchers could eventually apply this knowledge to improve gut health in people who are not born with a short intestine, such as people with obesity.

“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 partic- ular nutrient is causing the intestine to release the insulin-like hormone, the scientists can follow up by producing mutant flies lacking the receptor for that nutrient. By seeing the re- sponse in mutant flies, the researchers can isolate indi- vidual receptors and deter- mine what nutrient causes gut growth.

Ultimately, this research could be scaled up to appli- cations 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 re- search might also be applied in the op- posite direction: to slow intestine growth and limit calorie absorption in those with obesity.

Pruit is a member of the Cardiovas- cular Institute, the Child Health Re- search Institute, Stanford ChEM-H and the Stanford Neurosciences Institute.
There’s a good news/bad news story playing out around teen smoking. After years of decline, 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.

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. This was concerning because blunts contain nicotine, the 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 the idea that tobacco and marijuana is a way to reduce stress, and instead help adolescents find alternative stress-reducing strategies, such as exercise, healthy eating and so on.

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

The majority of marijuana and blunt users reported getting these from their friends, used them most often with friends 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 supposed benefits of marijuana, and how exposure to such ads was associated with a 6 percent increase in marijuana use. Adolescents who reported seeing ads for the supposed benefits of marijuana, and how exposure to such ads was associated with a 6 percent increase in marijuana use.

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 misconceptions about peer use might be effective. Studies have shown that changing perceptions that substance use is a normative behavior resulted in lower overall use. This approach can be employed by teachers, health educators, parents and health-care providers.

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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 norm attitudes that 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.

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 concerns.

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 investigators received $50,000 to $100,000 to fund projects:

**Pursevish Khatri, PhD, assistant professor of biomedical informatics research and of biomedical data science, for "Identifying patterns of patients at risk of developing severe dengue infection."**

**Stephen Quake, PhD, professor of bioengineering, and Sherrat Einar, MD, assistant professor of infectious diseases and of microbiology and immunology, for "Branching developmental pathways through high-dimensionality cell biology: Application to tissue- tropic dendritic cell development and the blood endothelium."

**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 Butler, MD, professor of pathology, and Juliana Iodoya, PhD, assistant professor of immunology, for "Branching developmental pathways through high-dimensionality cell biology: Application to tissue-tropic dendritic cell development and the blood endothelium."

**Holden Maecker, PhD, associate professor of medicine and a member of the Institute for Translational Genomics and Human Health, for "Genetic interrogation of patients at risk of developing severe dengue infection."**

**Steve Ghouse, PhD, associate professor of genetics, for "Regenerative potential of human fetal versus adult HSC transplant for acute lymphoblastic and macrophages heterogeneity."

**Matthew Lungren, MD, MPH, assistant professor of infectious diseases and an instructor of medicine, and Christopher Contag, PhD, professor of microbiology and immunology, for "In-vivo imaging and therapeutic strategies for bladder cancer in a mouse model."**

**Shirat Einav, PhD, assistant professor of medical genetics and of psychiatry and behavioral sciences, for "Heparin sulfate-IL-2 interactions in human sepsis.""**

**Hedwix Kuipers, PhD, assistant professor of pediatrics, for "Regenerative potential of human fetal versus adult HSC transplant for acute lymphoblastic and macrophages heterogeneity."**

**Sujan Ding, PhD, postdoctoral research fellow in gastroenterology, for "Genetic interrogation of host factors essential to neutropenic infection."**

**Gianluca Picci, PhD, postdoctoral scholar in microbiology and immunology, for "Investigating the genetics of 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 C5aR in human sepsis."**

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

**Hesham Peiris, PhD, postdoctoral scholar in developmental biology, for "Investigating the genetics of T-cell response to influenza vaccination in humans relates to the antibody response."**

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

**Christopher Contag, PhD, assistant professor of medicine and a member of the Institute for Translational Genomics and Human Health, for "Heparin sulfate-IL-2 interactions in human sepsis.""**

**Desiree Labeaud, MD, MSc, assistant professor of pediatric radiology, for "Heparin sulfate-IL-2 interactions in human sepsis.""**

**Matthew Lungren, MD, MPH, assistant professor of infectious diseases and an instructor of medicine, for "In-vivo imaging and therapeutic strategies for bladder cancer in a mouse model."**

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Scientists discover hormone that controls maturation of fat cells

By Erin Digita

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

The new findings were published Oct. 25 in Science Signaling. Around the body, fat deposits 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 that toggles the switch controlling whether fat cells normally make and secrete Adamts1. In adults, too much Adamts1 is seen in mice that are given glucocorticoids. Mice that are genetically engineered to make more Adamts1 in normal fat cells 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 cell's glucocorticoid response pathway. A cell-signaling molecule called plextrphin plays an important role in the pathway; blocking the molecule's signaling 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 their 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 tissue 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. 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.

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 questions. If we can 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, but when mice are given glucocorticoids.

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

Scientists honor medical student for helping to save man’s life

By Yasemin Sapkaloglu

A few months ago, as Laura Lu rumbled 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 doctor (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 stopped 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 raced over. She found an employee, a woman in her 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. Cells begin to die within a few minutes, the condition often results in death.

“Completely fine a few hours earlier”

“T here was a lot of shock,” she 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 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 study shows, 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,” she said. “I didn’t know whether he was going to be able to walk or to talk.”

Lu said that it was the first time she performed CPR on a person. Previously, she only had trained on mannequins. “This experience reminded me how important the information that we learn in class actually can 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.”

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.

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

By Yasemin Sapkaloglu

A few months ago, as Laura Lu rumbled 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 doctor (sic).”

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DNA-damage response links short telomeres, heart disorder

By Krista Conger

Progressively shortening telomeres — the protective caps on the ends 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” mice began to display the typical symptoms of the disease, including progressive muscle weakness, enlarged hearts and a significantly shortened life span.

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.

“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 cardiomyocytes continued to shorten, losing up to 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 help delay heart failure in mice.

“More research is clearly needed before we attempt to devise any new therapies for humans,” said Blau. “But these findings could have potential importance for other diseases...”

“...in which the disease process is not yet fully described. Treatment would provide a viable therapeutic opportunity for these diseases.”

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 contest, now in its 11th year, is scored just like the football game — with point systems for those who collect and those who receive it, you would think ‘you can’t just give any blood to any person’..."

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 system, that make it easier to do so. For example, concordant blood use among surgeons and nurses is displayed on a central computer screen, said Pham. "We take a snapshot daily..." she said. "...of the number of patients that are discharged in one day. That's the number of blood products that we need to deliver."

--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.

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 — most frequently, for surgeries or trauma care. While it’s not possible to predict precise needs, Pham said, “We take a snapshot daily of the blood product inventory...” she said. "...to determine what we are collecting. Our responsibility is to be good stewards of our blood supply..."
cases, wounds that had not healed for five years were successfully healed with the gene therapy. This was 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. This protein is needed to anchor the upper and lower layers of the skin together. As a result, the layers slide across one another due to the greatest 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 cells to stop blisters from forming and to heal wounds. 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 age 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 stop blisters from forming and to heal wounds. They also found that the protein continued to be expressed and that wound healing was improved during a year of follow up.

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.

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 patients with 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 call 723-7831.

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 member 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 point in providing therapy to patients. We had to discover the genes and proteins involved and the responsible mechanisms to understand what could be done to correct the 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.

Sickle

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 responses to the gene editing procedure, or the editing of DNA — so-called off-target effects. The effects of gene editing in general are impossible to predict.

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 might not 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 be indistinguishable from 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 Alfred Lane, MD; associate professor of medicine Ravanjna Majeti, MD, PhD; assistant clinical professor of dermatology Anupama Narla, MD, PhD; and professor of dermatology Thomas Leung, MD, PhD; professor of radiology and of pathology Kerri Rigger, MD, PhD; professor of dermatology Paul Khavari, MD, PhD; and professor emeritus of dermatology and of pediatrics Alfred Lane, MD.

This research was supported by the National Institutes of Health, the Epidermolysis Bullosa Research Partnership, the Stanford’s Department of Dermatology also supported the work.
Discrimination continued from page 1

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

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

We’ll also be interested in developing new tools to detect infectious diseases, 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 we would have to ship a blood sample to the CDC in Atlanta, which would dramatically slow the process of detection and identification of infectious agents. Certainly we’re interested in making this technology better and more routine.

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 were very concerned with 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 patients and establish their identity and the importance of their child’s health relative to all else, including their prejudice. This may be published, these physicians asserted, through acknowledging the discriminatory remarks and exploring underlying reasons for them.

However, four of the physicians said it was best to focus simply 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 safe learning and working environments and the need to be prepared to deal with discriminatory comments or situations.

What’s heartening in this study is that in a busy medical setting with a lot of demands, nobody really wants more training, but wants more training and feedback. The participants felt if they would like to have more on this topic, especially for one person said absolutely.

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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,” 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 Systems Biology. His five-year term began Sept. 1.

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 pain in children and adolescents with chronic pain.

SEDAR 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.

JAMES ZOU, 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.

Lloyd Minor, 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 the Stanford Center for Systems Biology. Please join me in thanking Tobias for his thoughtful leadership and exceptional service and congratulating James on his appointment.”

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 the laboratory of Chemical and Physical Biology, pursuing research as an under- graduate 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 regulating gene expression to the develop- ment of anticancer drugs that mimic cyclo- pamine 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.

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