INSIDE STANFORD MEDICINE

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CRISPR is a revolutionary gene-editing tool, but it's not without risk.
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Graduating med students meet their matches

By Tracie White

Victoria Boggiano, a soon-to-graduate Stanford medical student fresh out of scrubs and wearing a pink dress, had one word for how she was feeling at 8:30 a.m. March 16: "Petrified!"

And no wonder.

Projected onto giant screens behind the podium in Berg Hall, at the Li Ka Shing Center for Learning and Knowledge, was the countdown clock to her future: At that moment, the numbers read "15:00": 15 more minutes.

Fortunately, she wasn't alone.

Boggiano was one of 70 Stanford medical students awaiting envelopes on Match Day, when thousands of graduating medical students across the country find out at the same moment — noon Eastern time, or 9 a.m. on the West Coast — where they will spend the next three or more years of their lives as residents.

"When you open your envelopes today, I'm confident wherever you match, you will have the opportunity to grow and make contributions," said Lloyd Minor, MD, dean of the School of Medicine, who kicked off the event with calming words of gratitude for the students' years of hard work, praise for their successes and hope for their futures. "Take every advantage of every opportunity to become the very best that you can be."

As the clock continued to tick down, Neil Gesundheit, MD, interim senior associate dean for medical education and professor of medicine, stepped up to the podium to address the restless crowd.

"I've been told when you have a tense group like this, what helps is a song or dance or, even better, statistics. So here are a few," he said. Of the 70 Stanford medical students who applied for a residency, all matched somewhere. Four of them would graduate with master's degrees, six with PhDs and seven with MBAs. For the first time, the school would graduate more MD-MBAs than MD-PhDs, and for the second time in school history, twins were graduating. Then he got down to brass tacks.

STEVE FISCH

Twins Stephanie and Tiffany Chen on Match Day at the Li Ka Shing Center for Learning and Knowledge. A timer counted down the minutes and seconds until they and their fellow Stanford medical students could open envelopes with the letters informing them where they would spend their residencies.

Don't open the envelopes ... yet

"You cannot open the envelope until the countdown goes to zero," he said.

The matching process is a tradition that dates back to the 1950s, with residency assignments determined by a nonprofit organization, the National Resident Matching Program. The organization uses a computer algorithm to align the choices of the applicants with those of the residency programs.

Students began applying for residencies last summer. Then, they traveled nationwide in the fall to interview. And then they … waited.

"Being on the interview trail fully confirmed that family medicine was for me," said Boggiano, whose parents are both psychiatrists. "I interviewed at 16 programs, and at See MATCH, page 6

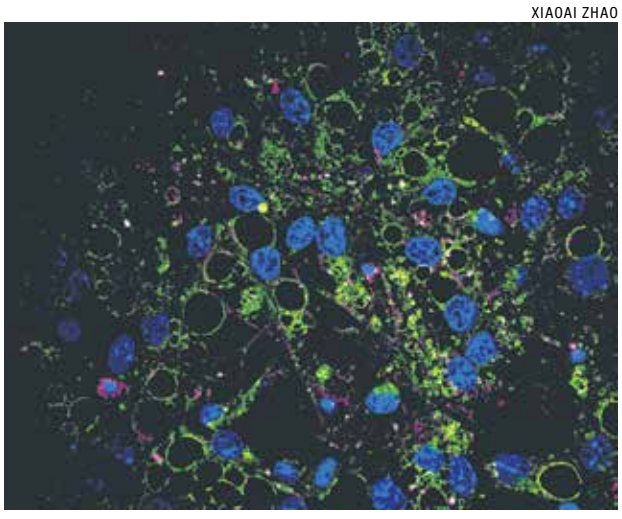
Clearing clumps of protein in aging neural stem cells boosts their activity

By Krista Conger

Young, resting neural stem cells in the brains of mice store large clumps of proteins in specialized cellular trash compartments known as lysosomes, researchers at the School of Medicine have found.

As the cells age, they become See PROTEINS, page 7

XIAOAI ZHAO



Resting neural stem cells (nuclei shown in blue) accumulate large protein aggregates (pink) in and around lysosomes (green).

Mysterious skeleton shows molecular complexity of bone diseases, according to a new study

By Hanae Armitage

A bizarre human skeleton, once rumored to have extraterrestrial origins, has gotten a rather comprehensive genomic work-up, the results of which are now in, researchers from the School of Medicine report.

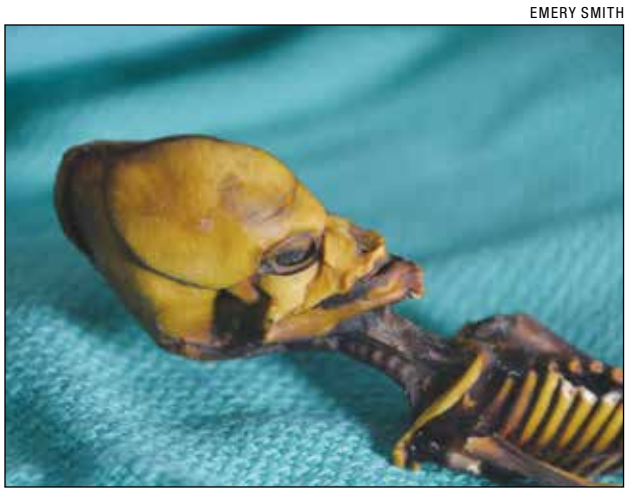
The findings stamp out any remaining questions about the specimen's home planet — it's without a doubt human — but more than that, the analysis answers questions about remains that have long been a genetic enigma.

After five years of deep genomic analysis, Garry Nolan, PhD, professor of microbiology and immunology at Stanford, and Atul Butte, MD, PhD, director of the Institute for Computational Health Sciences at University of California-San Francisco, have pinpointed the mutations responsible for the anomalous specimen. The researchers found mutations in not one but several genes known to govern bone development; what's more, some of these molecular oddities have never been described before.

"To me, it seems that when doctors perform analyses for patients and their families, we're often searching for one cause — one super-rare or unusual mutation that can explain the child's ailment. But in this case, we're pretty confident that multiple things went wrong," said Butte. It's an indication, he said, that looking for a single mutation, or even mutations that are already known to cause a particular disease, can discourage researchers from looking for other potential genetic causes and, in turn, potential treatments.

Nolan, who holds the Rachford and Carlota Harris Professorship, and Butte, a former Stanford faculty member who now holds the Priscilla Chan and Mark Zuckerberg Distinguished Professorship at UCSF, are senior authors of the study, which See SKELETON, page 7

EMERY SMITH



The 6-inch skeleton, nicknamed Ata, was discovered more than a decade ago in an abandoned town in the Atacama Desert of Chile.

Pioneering immunotherapy can find and kill elusive cancer cells

By Krista Conger

On a spring morning in April 2017, pediatric cancer specialist Kara Davis, DO, went to see Salvador De Leon, who was being treated at the Bass Center for Childhood Cancer and Blood Diseases at Lucile Packard Children's Hospital Stanford. The 11-year-old had leukemia, and he wasn't doing well. After three grueling years of therapy, his most recent relapse left only one course of action: an experimental treatment to seek out and destroy the cancer cells that had eluded conventional cancer treatments.

LESLIE WILLIAMSON

Kara Davis and Crystal Mackall are among the Stanford researchers investigating ways to make CAR-T cell therapy faster, cheaper, safer and more broadly applicable to leukemia and other types of cancer.

The treatment, known as CAR-T cell therapy, relies on a patient's own genetically modified immune cells to track down and attack the leukemia cells. Although some children with leukemia like Sal's have experienced years-long remissions after the therapy, about 30 percent of CAR-T cell recipients experience a temporary but potentially deadly side effect known as severe cytokine release syndrome.

Davis, an assistant professor of pediatrics at Stanford, was concerned because Sal had reacted poorly to previous rounds of chemotherapy. Did this mean he was likely to struggle with the CAR-T therapy as well?

"I was very worried," Davis said. "But there really weren't any other good options for Sal."

When she broached the subject of the new treatment with Sal's family, his mother, Maria De La Cruz, didn't hesitate. "If it has any chance of saving his life, we will do it," she recalled saying. "We will do whatever it takes."

CAR-T cell therapy is a rapidly emerging form of what's known as cancer immunotherapy, and it's been uncommonly successful. So successful, in fact, that in August the Food and Drug Administration fast-tracked its approval of a CAR-T cell treatment for children like Sal with relapsed or unresponsive acute lymphoblastic leukemia, or ALL. Marketed as Kymriah by Novartis, it was the first cell-based gene therapy approved by the FDA for use in humans. Lucile Packard Children's Hospital Stanford recently entered a contract with Novartis to become a certified treatment center, making it one of a small handful of California hospitals to offer Kymriah to children and young adults who may be helped.

> "Prior to CAR-T cell therapy, you would not even use that word, 'cure.'"

"Prior to CAR-T cell therapy, you would not even use that word, 'cure,'" Davis said.

"Instead I'd suggest other treatment options that might give the family a bit more time together."

The groundbreaking treatment significantly improves the likelihood of a cure for very sick patients. And because Stanford was one of the small group of centers involved in clinical testing for Kymriah, Packard Children's clinicians gained experience with patients like Sal before the treatment received FDA approval.

Sal's journey

On that April morning, Davis was desperately hoping to change Sal's world. As his modified T cells were infused through an IV line in his arm, Sal's care team monitored him closely for any negative reactions.

"But he just breezed through," Davis said. "He did so well, in fact, that I began to worry about the other possibility: that maybe the cells just weren't working. So we all just held our breath for the next month."

Sal's journey began in the spring of 2014, when he was 8 years old. The inveterate Oakland A's fan and video game lover had been struggling with what seemed to be allergies and was having trouble sleeping. Eventually, De La Cruz began to suspect there was something more seriously wrong.

"He was really tired, so I decided to take him to see the doctor," she recalls. "The next thing I knew, the doctor was asking me if I knew what leukemia was."

About 15,000 children are diagnosed with cancer each year in the United States; ALL accounts for about 3,000 of the childhood cancer diagnoses annually. Fortunately, it is one of the most treatable pediatric cancers. Ninety percent or more of children with the disease respond well to chemotherapy and quickly achieve remission. Many are cured completely. But the situation is much more dire for those who either don't respond to treatment, or whose cancer recurs. About 30-50 percent of these children die within five years. These statistics, coupled with the prevalence of the disease, place ALL on the top of the heap of deadly cancers in children, even though most patients are cured.

Unfortunately, after Sal was diagnosed with ALL in 2014, his doctors learned he was in a high-risk group. Sal's cancer cells harbored a dangerous genetic change known as a Philadelphia chromosome. Relatively rare in children with ALL, the presence of the Philadelphia chromosome leaves patients less able to achieve remission with standard chemotherapy and subject to quick relapse if remission is achieved. Five-year survival rates of these relapsed patients are only about 10 percent. These patients were given chemotherapy so strong it usually landed them in the intensive care unit.

In addition to the effects of the chemotherapy, Sal battled multiple infections that kept him in the ICU for over a month in November and December of 2014."We didn't know if he would make it through that period," said Catherine Aftandilian, MD, clinical assistant professor of pediatric hematology and oncology, who helped to treat Sal.

Not all cancer cells created equal

Genetic missteps like the Philadelphia chromosome are one reason children's tumors tend to be better than adults' at hiding out in normal tissue, escaping the hordes of immune cells that patrol our bodies looking for trouble. That's because kids' cancer cells have had less time to accumulate the many genetic mutations that build up over the course of a lifetime.

Instead, cancer cells in children often arise as a result of one or two powerful mutations. These alone are sufficient to send a cell spinning off the normal developmental track and into out-of-control cell division. But these lone-wolf mutations don't always create the types of red flags our immune system is looking for.

"In many ways, childhood cancers are the most elemental forms of cancer," said Crystal Mackall, MD, professor of pediatrics and of medicine, associate director of the Stanford Cancer Institute and director of the Stanford Center for Cancer Cell Therapy.

"A child's cells, which have tons of development and expansion potential, can go from being healthy to full-bore cancer seemingly overnight. And these cancers tend to grow quickly and aggressively. However, because these cancer cells are genetically more similar in terms of mutations to normal developing tissue than adult cancer cells are, it is harder for the immune system to recognize them as dangerous."

As a result, even some very promising immunotherapies in adults have been relatively unsuccessful in children. It's no good trying to amp up a nonexistent immune response, for example. Instead it has been necessary to craft a whole new approach.

"This is without a doubt a watershed moment in the history of cancer therapy," Mackall said.

"I've been working in the field of cancer immunotherapy for 40 years, and there's never been a more exciting time," said immunotherapy pioneer Ronald Levy, MD, professor of medicine and the Robert K. and Helen K. Summy Professor in the School of Medicine. "Some of the responses we're seeing with this treatment are nothing short of miraculous. The world of cancer immunotherapy has changed forever."

Weighing the costs

CAR-T cell therapy is time-consuming and expensive, with a price tag of hundreds of thousands of dollars per patient. Because Sal was participating in a clinical trial, there was no charge to his family for the cell therapy.

LESLIE WILLIAMSON

Salvador De Leon, who was treated with CAR-T cell therapy, and his mother, Maria De La Cruz.

And although it is costly to remove, genetically engineer and grow each patient's T cells in the laboratory, Novartis and Packard Children's are developing programs to ensure that no patient who needs Kymriah is turned away for financial reasons. Scientific advances may drive the cost down, too.

"I think we'll see a rapid evolution in the cost of the technology," Mackall said. "Did we ever imagine that we would one day have cellphones that can do what they do for the amount we pay now? This is a new field, and it's only going to get more affordable."

Hope for the future

Once Sal's engineered cells were infused, his

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STANFORD MEDICINE

Use of artificial intelligence in medicine raises ethical questions

By Patricia Hannon

Artificial intelligence is hard at work crunching health data to improve diagnostics and help doctors make better decisions for their patients. But researchers at the School of Medicine say the furious pace of growth in the development of machine-learning tools calls for physicians and scientists to carefully examine the ethical risks of incorporating them into decision-making.

In a perspective piece published March 15 in *The New England Journal of Medicine*, the authors acknowledged the tremendous benefit that machine learning can have on patient health. But they cautioned that the full benefit of using this type of tool to make predictions and take alternative actions can't be realized without careful consideration of the accompanying ethical pitfalls.

"Because of the many potential benefits, there's a strong desire in society to have these tools piloted and implemented into health care," said the lead author, Danton Char, MD, assistant professor of anesthesiology, perioperative and pain medicine. "But we have begun to notice, from implementations in nonhealth care areas, that there can be ethical problems with algorithmic learning when it's deployed at a large scale."

Among the concerns the authors raised are:

- Data used to create algorithms can contain bias that is reflected in the algorithms and in the clinical recommendations they generate. Also, algorithms might be designed to skew results, depending on who's developing them and on the motives of the programmers, companies or health care systems deploying them.
- Physicians must adequately understand how algorithms are created, critically assess the source of the data used to create the statistical models designed to predict outcomes, understand how the models function and guard against becoming overly dependent on them.
- Data gathered about patient health, diagnostics and outcomes become part of the "collective knowledge" of published literature and information collected by health care systems and might be used without regard for clinical experience and the human aspect of patient care.
- Machine-learning-based clinical guidance may introduce a third-party "actor" into the physician-patient relationship, challenging the dynamics of responsibility in the relationship and the expectation of confidentiality.

"We need to be cautious about caring for people based on what algorithms are showing us," Char said. "The one thing people can do that machines can't do is step aside from our ideas and evaluate them critically."

Sources of bias

In discussing designer intent, which is one source of bias, the authors pointed to private-sector examples of algorithms meant to ensure specific outcomes, such as Volkswagen's algorithm that allowed vehicles to pass emissions tests by reducing their nitrogen oxide emissions during the tests.

Danton Char

David Magnus

Nigam Shah

David Magnus, PhD, senior author of the piece and director of the Stanford Center for Biomedical Ethics, said bias can play into health data in three ways: human bias; bias that is introduced by design; and bias in the ways health care systems use the data.

"You can easily imagine that the algorithms being built into the health care system might be reflective of different, conflicting interests," said Magnus, who is also the Thomas A. Raffin Professor of Medicine and Biomedical Ethics. "What if the algorithm is designed around the goal of saving money? What if different treatment decisions about patients are made depending on insurance status or their ability to pay?"

The authors called for a national conversation about the "perpetual tension between the goals of improving health and generating profit … since the builders and purchasers of machine-learning systems are unlikely to be the same people delivering bedside care."

They also put the responsibility for finding solutions and setting the agenda on health care professionals.

"Ethical guidelines can be created to catch up with the age of machine learning and artificial intelligence that is already upon us," the authors wrote. "Physicians who use machine-learning systems can become more educated about their construction, the data sets they are built on and their limitations. Remaining ignorant about the construction of machine-learning systems or allowing them to be constructed as black boxes could lead to ethically problematic outcomes."

> "Artificial intelligence will be pervasive in health care in a few years."

The authors acknowledge the social pressure to incorporate the latest tools in order to provide better health outcomes for patients.

"Artificial intelligence will be pervasive in health care in a few years," said co-author Nigam Shah, MBBS, PhD, associate professor of medicine. But health care systems need to be aware of the pitfalls that have happened in other industries, he added.

Shah noted that models are only as trustworthy as the data being gathered and shared. "Be careful about knowing the data from which you learn," he said.

Could data become the doctor?

The authors wrote that what physicians learn from the data needs to be heavily weighed against what they know from their own clinical experience. Overreliance on machine guidance might lead to self-fulfilling prophesies.

For example, they said, if clinicians always withdraw care in patients with certain diagnoses, such as extreme prematurity or brain injury, machine-learning systems may learn that such diagnoses are always fatal. Conversely, machine-learning systems, properly deployed, may help resolve disparities in health care delivery by compensating for known biases or by identifying where more research is needed to balance the underlying data.

Magnus said the example of a current pilot study of an algorithm developed at Stanford to predict the need for a palliative care consultation illustrates how collaborative, careful consideration in the design of an algorithm and use of the data can guard against the misinterpretation of data in making care decisions.

Shah is helping to lead the pilot study. In this case, Magnus said, physicians and designers work closely to ensure that the incorporation of the predictions into the care equation includes guarantees that the physician "has a full understanding that the patient problems are answered and well-understood."

The insertion of an algorithm's predictions into the patient-physician relationship also introduces a third party, turning the relationship into one between the patient and the health care system.

It also means significant changes in terms of a patient's expectation of confidentiality.

"Once machine-learning-based decision support is integrated into clinical care, withholding information from electronic records will become increasingly difficult, since patients whose data aren't recorded can't benefit from machine-learning analyses," the authors wrote.

Magnus said the pressure to turn to data for answers is especially intense in fields that are growing quickly, such as genetic testing and sequencing.

"In a situation where you're looking for any evidence in informing your decision-making that you can get, and now you have all this genetics information and you don't know how to deal with," having clear data can be enormously helpful, he said.

Char, who is doing research funded by the National Institutes of Health on the ethical and social implications of expanded genetic testing of critically ill children, said it's important for health care professionals to figure out how to minimize negative outcomes of data-based decisions in all fields.

"I think society has become very breathless in looking for quick answers," he said. "I think we need to be more thoughtful in implementing machine learning."

Shah is assistant director of Stanford's Center for Biomedical Informatics Research and co-director of Spectrum, a research center funded by an NIH Clinical and Transitional Science Award. He is also a member of the Stanford Cancer Institute and the Stanford Neurosciences Institute. **ISM**

CAR-T

continued from page 2

physicians watched nervously for any signs of … well, anything.

"We were all so worried," Aftandilian said. "I kept waiting every day for him to get a fever, and he just didn't." After a month, Sal had another check of his bone marrow to search for the presence of any leukemia cells, and his care team finally let out their collective breath.

The cancer cells were gone.

"It was truly amazing," Davis said. "Maria had tears in her eyes when we told her." Now, researchers at Stanford, including Davis, Mackall and their colleagues, are investigating ways to make CAR-T cell therapy faster, cheaper, safer and more broadly applicable to other types of cancers. They're experimenting with combination therapies that target more than one molecule on the leukemia cells and also looking for new targets on cells in solid tumors. And, of course, they're closely following the progress of kids like Sal in ongoing clinical trials at Stanford.

"This is entirely unique," Mackall said. "It's something we cooked up in the lab. We've taken a powerful cell, and tricked it to go after a tumor by recognizing something it would normally ignore. And it turns out it works very well." While it's too soon to tell for sure whether Sal has been cured of his cancer, clinical data shows that some other children have remained in remission for years. And researchers are working to improve cancer immunotherapy options for children and adults with all types of cancer. For example, Mackall is supervising a clinical trial of CAR-T cells that can recognize more than one molecule, in the hope of packing a broader therapeutic punch. Levy is investigating ways to combine the CAR-T cells with other immunotherapy approaches that block naturally occurring immune system checkpoints that prevent the immune system from tackling the cancer.

"The future is going to be in combinations of therapies that work together," Levy said. Levy envisions the possibility of genetically engineering the T cells within a patient's body, eliminating the need to manipulate them in the laboratory and making the treatment faster, safer and cheaper, because it would no longer have to be customized for each patient.

"When I tell people that I treat kids with cancer, they often say, 'How can you do that; it must be the saddest job in the world,'" Davis said. "But it's not that to me at all. It's a very hopeful job, particularly now." **ISM**

Conference to showcase research on human immune monitoring

Stanford's Institute for Immunity, Transplantation and Infection is hosting a two-day conference on research on new technologies and analytic methods for human immunology.

The ITI Human Immune Monitoring Technology and Bioinformatics Conference is scheduled for 8 a.m.-5:45 p.m. March 30 and 8 a.m.-3 p.m. March 31 in Berg Hall at the Li Ka Shing Center for Learning and Knowledge.

Speakers will include more than a dozen Stanford faculty members, as well as faculty researchers from the Massachusetts Institute of Technology, the University of California-San Francisco, the Institute for Systems Biology, the Pasteur Institute and the Karolinska Institute.

The event is free, but attendance will be limited to 160. Prospective attendees must register online by March 26 or at the door if the conference isn't already filled. **ISM**

Target, delete, repair: The promises and perils of CRISPR

By Mark Shwartz

Once a month, David Sanchez, 15, comes to Lucile Packard Children's Hospital Stanford for an infusion of donor red blood cells. David was born with sickle-cell disease, an inherited disorder caused by a mutation in one gene among the roughly 20,000 in our DNA.

David's monthly infusions offer only temporary relief from the debilitating and potentially deadly complications of his disease. But what if his genetic disease — and thousands of others — could be cured by simply fixing the mutation? Researchers are betting they can with CRISPR, a powerful technology that allows scientists to quickly target, delete and repair any mutated sequence of DNA in any gene.

Other gene-editing tools have emerged in recent years, but none seems to match the precision, low cost and usability of CRISPR, which is rapidly transforming genetic research and has entered testing as a medical treatment.

"It's no exaggeration to say that CRISPR has been revolutionary," said Mark Mercola, PhD, a professor of cardiovascular medicine and a member of the Stanford Cardiovascular Institute. "With CRISPR, we can do genetic experiments that would have been unimaginable just a few years ago, not just on inherited disorders but also on genes that contribute to acquired diseases, including AIDS, cancer and heart diseases."

TIMOTHY ARCHIBALD

David Sanchez, who has sickle cell disease, at home with his grandmother Dolores Sanchez.

CRISPR was introduced to the world in 2012, and the technology has since generated a tsunami of research. Barely a week goes by without news of another CRISPR "breakthrough." But the rapid pace of discovery has raised questions about the regulation and oversight of this gene-altering tool.

Some fear that CRISPR will be used to create designer babies with desirable physical traits and talents. Others are concerned about ongoing experiments to alter the DNA of disease-spreading insects and to genetically enhance crops and livestock, in part because of unintended impacts on the environment. Laboratories have already used CRISPR to engineer bigger tomatoes, longer-lasting mushrooms and leaner pigs for CRISPR bacon — items that may one day appear on your grocery shelf.

"When it comes to experiments on animals, plants and microbes, two things worry me," said Stanford bioethicist Hank Greely, JD, a professor of law. "One is the intentional misuse of CRISPR. The other is that people with good intentions will inadvertently cause harm."

"But for treating classic genetic diseases like sickle cell, I think CRISPR will be transformative," he added, "and that's a great thing."

Living day to day

Our genes are encoded with instructions for making proteins. The "letters" in that genetic code are four chemical building blocks — adenosine, cytosine, guanine and thymine, known simply as A, C, G and T.

The DNA double helix in humans consists of 6 billion of these building blocks arranged in a specific order, but a single error in that sequence can be deadly. Scientists have identified more than 10,000 inherited diseases caused by a single defective gene, many incurable, like cystic fibrosis, hemophilia, muscular dystrophy and Tay-Sachs disease.

In sickle-cell disease, for example, one building block — an A — is converted to T in a gene that makes hemoglobin, the protein in red blood cells that delivers oxygen from the lungs to the rest of the body.

"It's like having one typo in a book containing 6 billion letters," said Matthew Porteus, MD, PhD, an associate professor of pediatrics at Stanford, and a scientific co-founder and advisory board member of CRISPR Therapeutics, a company that uses CRISPR technology. "We spent six years trying to repair that one mutation using older gene-editing technologies, but with CRISPR, we finally had a tool that was much easier to use and far more efficient."

Hemoglobin helps red blood cells maintain a smooth, round shape, which allows them to move freely through blood vessels. But in sickle-cell disease, the damaged gene produces stiff, sticky red blood cells that collapse into a sickle shape after delivering oxygen. The sickled cells often clump together, causing excruciating pain and blocking the flow of oxygen-rich, normal red blood cells to vital organs.

For David Sanchez, prolonged blockages have led to chronic kidney disease and permanent damage to his spleen. By age 10, he had been admitted to Packard Children's Hospital twice with acute chest syndrome, a potentially fatal condition that occurs when sickled cells block the flow of oxygen to the lungs.

"The hospital is my second home. I always have good doctors here," said David, who has also experienced back pain so severe he could barely walk. "He's been poked and poked since infancy," said Dolores Sanchez, David's grandmother and legal guardian.

"We live day by day and try to give him the best quality of life. Just let him be a child," she said.

Sickle-cell disease affects about 100,000 people in the United States, primarily African-Americans, and millions more worldwide. About 15 percent of patients can be cured with a bone-marrow transplant from a healthy sibling. "Even with the best care, patients in the U.S. typically die in their mid-40s. In low-income countries where medical care is poor, many children die before age 5," Porteus said.

But for David and millions of others, the most promising approach may be genetic engineering. Next year, Porteus hopes to launch Stanford's first clinical trial of CRISPR. The goal: correct the genetic typo that causes sickle-cell disease so that patients like David can live long, healthy lives.

Gift from Mother Nature

The CRISPR revolution sweeping through laboratories around the world has humble roots that go back billions of years.

"CRISPR is a gift from Mother Nature," said Stanley Qi, PhD, an assistant professor of bioengineering and of chemical and systems biology, and the scientific co-founder of Refuge Biotechnologies Inc., which uses CRISPR technology. "It was first observed in 1987, when researchers in Japan noticed a weird, repeating sequence in the DNA of *E. coli* bacteria."

Later studies found repeating segments of DNA in other microbial species. These mysterious repeats consisted of a short sequence of genetic code and a similar sequence in reverse. This peculiar palindrome pattern was dubbed CRISPR — "clustered regularly interspaced short palindromic repeats." Further research led to the discovery of CRISPR-associated (Cas) genes, which produce Cas enzymes that can slice through DNA. Scientists eventually realized that bacteria have been using CRISPR-Cas complexes for billions of years to attack and destroy enemy viruses, and that this ancient bacterial immune system could be adapted for use in genetic engineering. In 2012, UC-Berkeley professor Jennifer Doudna, PhD, and her colleagues showed how CRISPR and the enzyme Cas9 could be quickly engineered to find and cut specific sequences of DNA in a test tube. The following year, separate studies by Doudna and others — including an MIT team led by Stanford alumnus Feng Zhang, PhD — demonstrated that CRISPR-Cas9 could be programmed to edit human DNA.

"These landmark studies demonstrated the power of CRISPR-Cas9 to target and delete any sequence of DNA in the human genome," said Qi, a former graduate student in Doudna's lab. "It's a simple process. To fix a damaged gene, you begin by designing an RNA molecule that matches the mutated DNA sequence in that gene. You then combine the RNA with a Cas9 enzyme, which can cut through DNA like a sharp scissors. The RNA acts like a very fast GPS — it guides the Cas9 enzyme to the mutated DNA sequence. The enzyme then binds to the sequence and deletes it."

The final repair can be done using a benign virus that's engineered to deliver and insert the correct DNA sequence into the edited gene. The result is a normal gene free of the disease-causing mutation.

Older gene-editing tools use proteins instead of RNA to target damaged genes. But it can take months to design a single, customized protein at a cost of more than $1,000. With CRISPR, scientists can create a short RNA template in just a few days using free software and a DNA starter kit that costs $65 plus shipping. Unlike protein-based technologies, the RNA in CRISPR can be reprogrammed to target multiple genes.

Clinical trial

The proposed Stanford clinical trial will focus on the stem cells in our bone marrow that produce red blood cells.

People with sickle-cell disease have two defective hemoglobin genes in their stem cells, one from each parent. Together, the two defective genes are what cause red blood cells, which are normally disc-shaped and flexible, to become stiff and sticky as they mature.

People who inherit one defective gene and one normal gene have what is known as sickle-cell trait, a condition that affects about 3 million Americans. Most of their red blood cells are normal, allowing them to lead healthy lives free of sickle-cell disease. However, the abnormal hemoglobin gene in their DNA can be passed on to their children.

In his trial, Porteus plans to repair and replace defective blood stem cells in patients with sickle-cell disease. The idea is to transform the patients into healthy people with sickle-cell trait by converting their defective stem cells with two abnormal hemoglobin genes into stem cells with just a single abnormal gene.

CRISPR's job will be to remove the mutated DNA sequence from one of the genes.

"Our first step will be to design CRISPR-Cas9 to locate and delete the DNA mutation," Porteus said. "But that won't fix anything. We also have to engineer a virus to deliver the correct sequence of normal DNA."

Once the gene has been repaired, the newly modified stem cells with sickle-cell trait will be injected back into the patient's bloodstream. Ideally, some will find their way into the bone marrow and start cranking out millions of healthy red blood cells.

"We'll probably have to use chemotherapy to create a space in the patient's bone marrow for the corrected stem cells to be taken up," Porteus said. "The repaired stem cells could create enough normal red blood cells for the patient to be symptom-free for life," he added. "That's the ultimate goal."

70 percent threshold

The CRISPR process doesn't have to be perfect to be effective, Porteus said. That's because symptoms of the disease occur only if the proportion of sickled cells in the bloodstream is above 30 percent. If at least 70 percent of the red blood cells are healthy, the patient is symptom-free.

"Having 20 percent corrected stem cells in the bone marrow will probably be

sufficient for most patients to get above the 70 percent threshold," Porteus said. "That's because healthy red blood cells live about five times longer than diseased cells and quickly outnumber them."

Monitoring the modified stem cells to make sure they are producing enough healthy red blood cells will be crucial, he added.

"The proof will come when we follow the patients over time and see whether they have any symptoms of the disease," Porteus said. "They could remain symptom-free, or they might need additional treatments. Some things we'll know in a month, others in 10 years."

Patients like David are well aware of the 70 percent target. Every Monday, he undergoes a blood test at a hospital clinic to measure his sickle-cell count. The results determine how much healthy donor blood he will receive at his next infusion, which is part of a three-hour procedure known as apheresis, in which David's diseased red blood cells are removed and replaced with normal donor cells.

But the benefits of the infusion last only about a month, during which time his defective stem cells continue to function, producing more diseased red blood cells.

Prior to his infusion in November, David's count had risen to 24 percent, slightly below the level that triggers new symptoms. But after the infusion, the proportion of sickled cells dropped to just 12 percent.

Staying above the 70 percent threshold has reduced many of David's symptoms. But last spring, intense headaches forced him to withdraw from school. He was diagnosed with moya-moya disease, a potentially lethal condition caused by blockage in the arteries to his brain. He had surgery at Packard Children's to bypass the blocked arteries and restore blood flow.

"The brain surgery saved his life," said Jennifer Andrews, MD, MSc, David's primary doctor, a clinical associate professor of pathology and of pediatrics. "Without it, he could have had a major stroke."

His grandmother recalled the day of the procedure: "Before he went into surgery I said, 'Baby, aren't you scared?'" she said. "He said, 'No, Nana, would you rather take care of me like I am now, or after I have a stroke?' He's a very compassionate child."

David recovered from the surgery and has enrolled as a freshman in an online high school that lets him study at his own pace. That way he doesn't have to worry about missing class because of lengthy medical procedures or when symptoms recur.

If the CRISPR clinical trial at Stanford is successful, monthly infusions of donor red blood cells for people with sickle-cell disease could be a thing of the past.

"I think it's great that people are working with CRISPR to cure sickle cell and other diseases," David said. "It's really cool that they could come up with something like this. So many people have lives that could be so much better."

Designer babies

Clinical trials of CRISPR like the one Porteus is proposing have broad public support, in part because using CRISPR in adults and children would alter their DNA, but not that of their offspring.

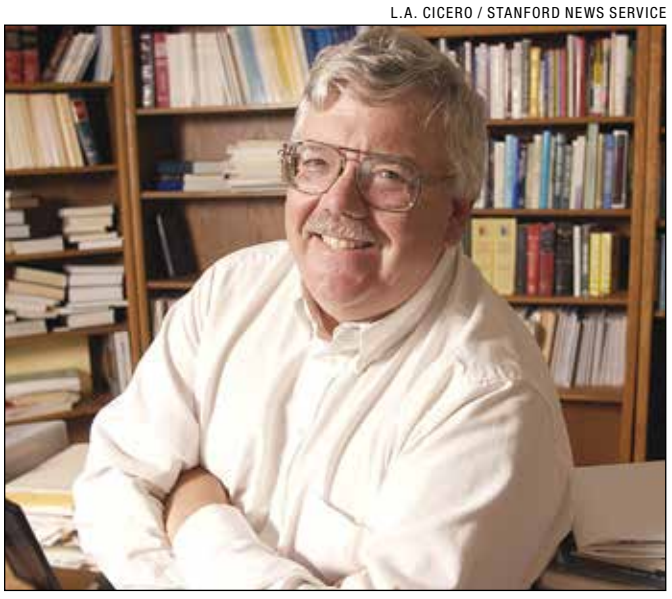
Editing human embryos to repair disease-causing genes is far more controversial. One concern is that CRISPR occasionally targets and removes the wrong gene. One off-target event could have serious consequences for newborns and their descendants.

"The idea of editing human embryos makes a lot of people queasy, and it should," Mercola said. "CRISPR isn't perfect, and when you alter embryonic DNA, the results are passed from one generation to the next."

Public anxiety was heightened in 2015 when scientists in China used CRISPR to edit human embryos for the first time. Although the experimental embryos were not viable, some worried that fertility clinics would start using CRISPR to genetically engineer children with traits parents might want, like making them stronger, taller or smarter.

"People are most worried about enhancement — using CRISPR to give babies superpowers," Greely said. "But we don't know now any genes that give people superpowers. For practical and regulatory reasons, we're not going to be CRISPRing embryos and making designer babies any time soon."

L.A. CICERO / STANFORD NEWS SERVICE



TIMOTHY ARCHIBALD

Bioethicist Hank Greely (left) said he believes CRISPR will be "transformative" for the treatment of "classic genetic diseases like sickle cell," but said the technique also makes it easier for people with bad intentions to do harm. Clinician-researcher Matthew Porteus (right) hopes to launch Stanford's first clinical trial of CRISPR. The goal: correct the genetic typo that causes sickle-cell disease.

"CRISPR is a gift from Mother Nature."

Greely also sees little justification for using CRISPR in embryos to prevent disease. "Very few people will need to do gene editing to have healthy babies," he said. "Almost every genetic disease can be avoided using preimplantation genetic diagnosis. Rather than changing genes in an embryo, you just select an embryo that doesn't have the dangerous genes. PGD has been around for almost 30 years. It's safe and effective."

In a 2017 report, the National Academy of Sciences recommended that, for now, CRISPR and other gene-editing tools be permitted only in human clinical trials aimed at curing and preventing serious diseases, not enhancing babies.

Proceed with caution

Sickle-cell disease seems well-suited for CRISPR gene therapy because it targets a specific type of cell, according to the 2017 National Academy of Sciences report. Other inherited diseases, such as cystic fibrosis and muscular dystrophy, may be more difficult to treat because they affect different cell types in different organs. Despite these challenges, a number of labs are using CRISPR to find cures for these and other genetic diseases in adults and children.

"For what we're doing, CRISPR has made things easier," said Porteus, who served on the NAS report committee. "The momentum for developing new gene therapies is incredible. We want to move fast because the patients deserve that, but we want to move carefully. We don't want to do something that causes a huge setback."

Gene therapy did suffer a major setback in 1999 when an 18-year-old man with an inherited liver disease died during a clinical trial at the University of Pennsylvania. Researchers had injected what was thought to be a harmless virus carrying a modified gene into the man's liver. But the virus ran amok, triggering a severe immune response, and the young man died four days later.

Before then, gene therapy had been considered a promising treatment for many diseases, but the clinical-trial death stopped other researchers in their tracks. Fast forward to 2016, when a different group from the University of Pennsylvania asked a federal panel to green-light the first-ever clinical trial using CRISPR. The trial was designed to genetically alter immune cells in cancer patients, then reinject the modified cells to see if they would improve the immune system's ability to fight off the disease.

Hearings were held before the Recombinant DNA Advisory Committee, a panel of experts that advises the director of the National Institutes of Health on whether to approve federally funded gene-transfer trials.

"There was a lot of trepidation at the hearings, in part because the cancer protocol is so complex," said Stanford bioethicist Mildred Cho, PhD, who is a member of the advisory committee. "It requires manipulating lots of different systems at the same time, especially the immune system, which is not fully predictable."

Unresolved questions about the 1999 fatality persisted throughout the hearings, but the committee ultimately recommended that the clinical trial proceed using CRISPR.

"In the 1999 case, a genetically altered virus was infused directly into the patient's liver, so there was little control on where it spread through the bloodstream," said Cho, a professor of pediatrics and of medicine. "But most CRISPR protocols are *ex vivo* — they take the cells out of the body, manipulate them and then put them back. That, at least, allows for some kind of risk assessment to see if there are any off-target gene modifications, or if they've turned the immune cells into cancer cells by accident."

Even if CRISPR proves successful, Cho worries that for many patients, the financial cost will be prohibitive.

"Gene therapy is not the same as taking a pill from the pharmacy," she said. "It's more like getting an organ transplant. It's a very complex procedure. Cancer immunotherapy already costs in the hundreds of thousands of dollars per year. There's no way that gene-edited treatments are going to be any less expensive."

Runaway evolution

Cho is also concerned about using CRISPR to control entire populations of disease-spreading animals, like mosquitoes that carry malaria and mice that transmit Lyme disease. Researchers are exploring ways of altering the DNA in these and other fast-breeding species so that future generations cannot spread disease.

But attempts to manipulate nature, though well-meaning, sometimes backfire.

"We don't have the ability to control runaway evolutionary changes to wild populations," Cho said. "There's no regulatory framework to test mosquitoes and other modified organisms. Once they're released in the wild, it's hard to reverse any inadvertent effects."

CRISPR also makes it easier for people with bad intentions to do harm, Greely said.

"Smallpox has been eradicated in the wild," he said. "But if you want to make a biological weapon, you can use CRISPR to turn ordinary cowpox virus into smallpox."

What's needed, Greely said, are well-thought-out, well-enforced federal regulations that make it difficult for CRISPR to be misused accidentally or intentionally.

"The Obama administration listed gene editing as one of the four biggest threats to the country," he said. "It might be ISIS or North Korea. I guarantee that there are people in Washington, D.C., very worried about this."

CRISPR Model T

Still, the promise that CRISPR offers keeps researchers focused on the future. Beyond treating individual patients, the most important application of CRISPR may lie in the discovery of new drugs for dozens of intractable diseases, Mercola said.

"We're just scratching the surface in the drug-target space," he said. "For me, that's where this field is going. CRISPR is a great example of how basic research can lead to something of tremendous utility in a record amount of time."

At Stanford, recruitment of participants for the sickle-cell clinical trial could begin early next year. But more work is needed to demonstrate that stem cells altered with CRISPR are ready to be tested in people. Last year, Porteus received a $5.2 million grant from the California Institute for Regenerative Medicine to fund that additional research.

Donated human stem cells are now being processed at the Stanford Laboratory for Cell and Gene Medicine, a large facility dedicated to making biological materials that meet the rigorous federal standards for clinical trials, including a high level of sterility and a strict protocol for chain of custody.

"Before the lab opened in 2016, there was no way for us to conduct an entire clinical trial at Stanford," Porteus said. "We'd have to send the stem cells to a company off campus for processing. But the new lab demonstrates a major commitment by Stanford to be at the forefront of gene therapy just as this promising field is emerging."

Greely compares the invention of CRISPR today to the rollout of the Ford Model T a century ago. "The Model T was cheap and reliable, and before long everybody had a car and the world changed," he said. "CRISPR has made gene editing cheap, easy and accessible, and therefore more common. I think it's going to change the world. Exactly how beats me." ISM

Match

continued from page 1

every single one, I thought, 'This is my place.'" Boggiano, who also holds a master's degree in public health from the University of California-Berkeley, said that wherever she ended up, her goals would be the same.

"I want to help empower communities to better understand their health so that they can help guide improvements in health-care settings," she said.

Quiet descends

The room quieted down as the students, many dressed in skirts and heels, or suits and ties, walked over to their advisers to pick up their envelopes.

The countdown clock showed just a few seconds remaining.

"Let's do the countdown together," Gesundheit said. Boggiano bounced up and down on her toes, her two closest friends nearby. "Five, four, three, two…." Confetti flew through the air as "Celebration," by Kool & The Gang, blared on speakers.

Chao Long burst into tears when she found out she had matched at Johns Hopkins University in plastic surgery. Grinning, she hugged her parents, as well as her boyfriend and her boyfriend's sister, both of whom are Stanford medical students.

Boggiano opened her envelope, clapped her hand over her mouth and started to cry. Then she held up the letter for everyone to see and hugged her friends. She'll be heading to the University of North Carolina-Chapel Hill — her first choice. **ISM**

STEVE FISCH

STEVE FISCH

STEVE FISCH

(Above) Victoria Boggiano matched in family medicine at the University of North Carolina-Chapel Hill, and Chao Long matched in plastic surgery at Johns Hopkins University. (Right) Lance Middleton holds up the notification that he matched in psychiatry at UC-San Francisco. (Top right) Dean Lloyd Minor spoke to the medical students before they opened their Match Day envelopes.

Health risk posed by guns is focus of Stanford Medicine teach-in

By Erin Digitale

Medical schools are uniquely positioned to teach current and future physicians about the health risks posed by guns, and to study how to reduce gun violence, said Daniel Bernstein, MD, associate dean for education at the medical school, in his opening remarks at a March 14 teach-in on campus addressing gun violence.

"One of the other missions of a medical school is to encourage and foster dialogue," he said. "There's no way to move forward on an issue as politically charged as this one without learning how to talk with our colleagues and friends about it."

The teach-in, "Gun Violence and Public Health: What We Know," included presentations on the epidemiology of gun violence, the financial cost of gun violence, the laws and regulations governing gun ownership in the United States, a trauma surgeon's perspective on gun injuries, and a pediatrician's call to action on the issue. Among the highlights:

• Understanding the national gun-violence epidemic requires delving into specifics, said Jahan Fahimi, MD, PhD, assistant clinical professor of emergency medicine at the University of California-San Francisco. "Are we talking injury or death? Homicides or suicides? Black or white? These three [categories], at the very minimum, are needed to get us to a place of understanding the scope of the problem in a more nuanced way," he said. He showed data indicating that gun deaths among African-Americans are primarily homicides. However, most gun deaths, and the majority of those among white Americans, are suicides.

ERIN DIGITALE

Panelists spoke March 14 at a teach-in on campus titled "Gun Violence and Public Health: What We Know."

• Stanford trauma surgeon Lisa Knowlton, MD, assistant professor of surgery, spoke about her experiences caring for gunshot victims. "As trauma surgeons, we like to think we are prepared for anything, but there are few injuries as violent as those from firearms," she said. Knowlton took the audience through the process of assessing and caring for a gunshot victim, enumerating the difficulties of stabilizing these patients and the priorities in trauma surgery for treating gunshot wounds. Patients who survive the initial surgery face "multiple surgeries, prolonged stays in the hospital, complications, loss of work, depression, mental health issues, PTSD; the impact can really be very devastating even if they do manage to leave the hospital alive," Knowlton said.

• The financial cost of gun injuries can be measured many different ways, with the annual total cost across the country estimated at $174-$229 billion, Stanford medical student Sarabeth Spitzer told the audience. Last year, Spitzer was the lead author of a study of the costs of initial hospitalizations for gun injuries, which totaled $734.6 million per year nationwide. Other costs, such as lost wages or the toll on quality of life following a gunshot injury, are harder to measure, she said. We also need clearer information on who bears the costs, which now typically land on gunshot victims, insurance companies and taxpayers. "The more reliable and transparent the data, the more informed public health decisions can be," Spitzer said.

• The United States has an array of gun laws that are not easy to explain or navigate, David Studdert, LLB, ScD, MPH, professor of medicine and of law, told the audience. "Most of these laws do not exist at a federal level," he said. "A state like California is a national leader in implementing and formulating such laws, while others such as Virginia and Wyoming have virtually none." He also described 2017 Pew Survey data that show widespread agreement between gun owners and nonowners on several proposed gun control measures, such as expanding background checks to include private gun sales and banning people from carrying concealed guns without a license.

• Pediatrician Michelle Sandberg, MD, of Santa Clara Valley Medical Center, explained how physicians can advocate for gun safety with their patients. Doctors should broach the subject of gun safety from a health perspective, Sandberg said. "Firearm counseling should be nonambiguous and nonjudgmental, like counseling about medication safety or storing poisons," she said. She also encouraged physicians to promote the ASK campaign, in which parents ask anyone who might be supervising their children, "Is there an unlocked gun where my child plays?"

Guns don't make families safer

At the end of the forum, several audience members asked questions about specific measures to reduce gun deaths in the United States. In response, Studdert emphasized the need to change prevailing ideas about firearms. Those with guns in the home are 22 times more likely to injure themselves or a family member than to use it in self-defense. And yet, he said, average gun owners typically have purchased a firearm because they think it keeps their families safer.

"The evidence shows that no, it doesn't, and the best thing we could do would be to convince them otherwise," Studdert said. "Clinicians clearly have a role to play in that changing of hearts and minds." **ISM**

Skeleton

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was published online March 22 in *Genome Research*. Sanchita Bhattacharya, a bioinformatics researcher at UCSF, is the lead author.

A human? A primate? An alien?

The skeleton, nicknamed Ata, was discovered more than a decade ago in an abandoned town in the Atacama Desert of Chile. After trading hands and eventually finding a permanent home in Spain, the mummified specimen started to garner public attention. Standing just 6 inches tall — about the length of a dollar bill — with an angular, elongated skull and sunken, slanted eye sockets, the internet began to bubble with otherworldly hullabaloo and talk of ET.

"I had heard about this specimen through a friend of mine, and I managed to get a picture of it," Nolan said. "You can't look at this specimen and not think it's interesting; it's quite dramatic. So I told my friend, 'Look, whatever it is, if it's got DNA, I can do the analysis.'"

Garry Nolan

With the help of Ralph Lachman, MD, a professor of radiology at Stanford and an expert in a type of pediatric bone disease, Nolan set the record straight. Their analysis pointed to a decisive conclusion: This was the skeleton of a human female, likely a fetus, that had suffered severe genetic mutations. In addition, Nolan saw that Ata, though most likely a fetus, had the bone composition of a 6-year-old, an indication that she had a rare, bone-aging disorder.

To understand the genetic underpinnings of Ata's physicality, Nolan turned to Butte for help in genomic evaluation. He accepted the challenge, running a work-up so comprehensive it nearly rose to the level of patient care. Butte noted that some people might wonder about the point of such in-depth analyses.

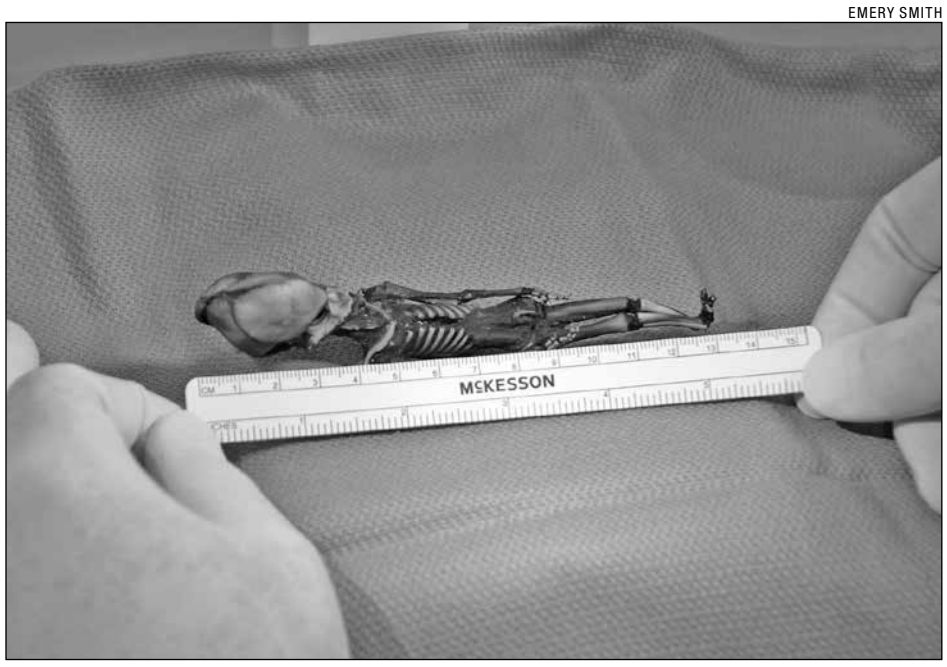
"We thought this would be an interesting exercise in applying the tools that we have today to really see what we could find," he said. "The phenotype, the symptoms and size of this girl were extremely unusual, and analyzing these kinds of really puzzling, old samples teaches us better how to analyze the DNA of kids today under current conditions."

New insights through old skeleton

To understand the genetic drivers at play, Butte and Nolan extracted a small DNA sample from Ata's ribs and sequenced the entire genome. The skeleton is approximately 40 years old, so its DNA is modern and still relatively intact. Moreover, data collected from whole-genome sequencing showed that Ata's molecular composition aligned with that of a human genome. Nolan noted that 8 percent of the DNA was unmatchable with human DNA, but that was due to a degraded sample, not extraterrestrial biology. (Later, a more sophisticated analysis was able to match up to 98 percent of the DNA, according to Nolan.)

The genomic results confirmed Ata's Chilean descent and turned up a slew of mutations in seven genes that separately or in combinations contribute to various bone deformities, facial malformations or skeletal dysplasia, more commonly known as dwarfism. Some of these mutations, though found in genes already known to cause disease, had never before been associated with bone growth or developmental disorders.

EMERY SMITH



After sequencing Ata's genome, researchers found mutations in seven genes that separately or in combinations contribute to various bone deformities, facial malformations or skeletal dysplasia.

Knowing these new mutational variants could be useful, Nolan said, because they add to the repository of known mutations to look for in humans with these kinds of bone or physical disorders.

"For me, what really came of this study was the idea that we shouldn't stop investigating when we find one gene that might explain a symptom. It could be multiple things going wrong, and it's worth getting a full explanation, especially as we head closer and closer to gene therapy," Butte said. "We could presumably one day fix some of these disorders, and we're going to want to make sure that if there's one mutation, we know that — but if there's more than one, we know that too."

Other Stanford authors of the study are graduate student Alexandra Sockell; senior research scientist Felice Bava, PhD; and Carlos Bustamante, PhD, professor of biomedical data science and of genetics.

Researchers at UCSF, Roche Sequencing Solutions, National Autonomous University of Mexico and Ultra Intelligence Corporation also contributed to the work.

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

The study was supported by the Lucile Packard Foundation for Children's Health, UCSF endowment funds and the Human Frontier Science Program.

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

Proteins

continued from page 1

less proficient at disposing of these protein aggregates, and their ability to respond readily to "make new neurons" signals wanes. Restoring the ability of the lysosomes to function normally rejuvenates the cells' ability to activate, the researchers found.

The discovery of the aggregates in young stem cells was unexpected, in part because similar aggregates are associated with the development of neurodegenerative diseases, such as Alzheimer's. It also highlights the importance of maintaining precise control over the protein production and disposal process throughout the life and activation status of neural stem cells.

"We were surprised by this finding because resting, or quiescent, neural stem cells have been thought to be a really pristine cell type just waiting for activation," said Anne Brunet, PhD, professor of genetics. "But now we've learned they have more protein aggregates than activated stem cells, and that these aggregates continue to accumulate as the cells age. If we remove these aggregates, we can improve the cells' ability to activate and make new neurons. So if one were able to restore this protein-processing function, it could be very important to bringing older, more dormant neural stem cells 'back to life.'"

A paper describing the research was published March 15 in *Science*. Brunet, an associate director of Stanford's Paul F. Glenn Center for the Biology of Aging, is the senior author. Postdoctoral scholar Dena Leeman, PhD, is the lead author.

Resting versus active neural stem cells

The researchers began their studies by looking to see what difference there might be, if any, between the gene-expression profiles of resting neural stem cells and those that had been activated in response to an outside signal to launch the process to make new neurons. They also compared how the cells changed as they aged.

Leeman isolated several populations of cells for study from the brains of both young and old mice, including resting neural stem cells, activated neural stem cells and the neural cell progenitors that arise from activated stem cells. She found that resting stem cells expressed many lysosome-associated genes, while activated stem cells expressed genes associated with a protein complex involved in protein destruction called a proteasome. Strict control of production and disposal allows cells to maintain the necessary protein inventory to carry out needed cellular functions.

GREGG SEGAL

Anne Brunet is senior author of the study, which made an unexpected finding: Young, resting neural stem cells have large protein clumps often associated with neurodegeneration.

When Leeman stained young resting and activated neural stem cells with a dye that binds to protein aggregates, she was surprised to find the resting stem cells stained more brightly, despite the fact that resting cells have a lower rate of protein production. Leeman also found that the young resting neural stem cells accumulated these protein aggregates in their large lysosomes relatively slowly compared with their activated counterparts.

"We were really struck by the differences between resting and activated stem cells in the expression of genes involved in protein quality control," said Brunet. "The fact that these young, pristine resting stem cells accumulate protein aggregates makes us wonder whether they actually serve an important function, perhaps by serving as a source of nutrients or energy upon degradation."

Old resting stem cells, Leeman found, express fewer lysosome-associated genes and begin to accumulate even higher levels of protein aggregates.

"It's almost as if these older cells lose the ability to store, or park, these aggregates," said Brunet. "We found that artificially clearing them by either activating lysosomes in older cells or subjecting them to starvation conditions to limit their protein production actually restored the ability of these older resting stem cells to activate."

The researchers plan to continue their studies to learn what types of proteins might be contributing to the aggregates to better understand why activated neural stem cells appear to favor proteasomes over lysosomes and to determine how the regulation of protein aggregation becomes disrupted during aging.

'Are they good or bad?'

"We'd like to know whether the aggregated proteins are the same in the young and old cells," said Brunet. "What do they do? Are they good or bad? Are they storing factors important for activation? If so, can we help elderly resting stem cells activate more quickly by harnessing these factors? Their existence in young cells suggests they may be serving an important function."

Other Stanford authors are former postdoctoral scholars Katja Hebestreit, PhD, and Ashley Webb, PhD; postdoctoral scholars Tyson Ruetz, PhD, Salah Mahmoudi, PhD, and Xiaoai Zhao, MD, PhD; graduate students Andrew McKay, Robin Yeo and Ben Dulken; former graduate student Elizabeth Pollina, PhD; laboratory manager Keerthana Devarajan; Thomas Rando, MD, PhD, professor of neurology and neurological sciences; and Judith Frydman, PhD, professor of genetics and of biology.

The research was supported by the National Institutes of Health, the National Science Foundation, the Glenn/American Federation for Aging Research, Stanford Bio-X, a National Defense Science and Engineering Graduate Fellowship and a Stanford cancer biology training grant.

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

Christopher Dawes, CEO of Stanford Children's Health, to retire

By Kate DeTrempe

Christopher Dawes, president and CEO of Lucile Packard Children's Hospital Stanford and Stanford Children's Health, announced his retirement on March 20 after nearly 30 years with the organization.

Dennis Lund, MD, chief medical officer for Stanford Children's Health, has been appointed interim CEO.

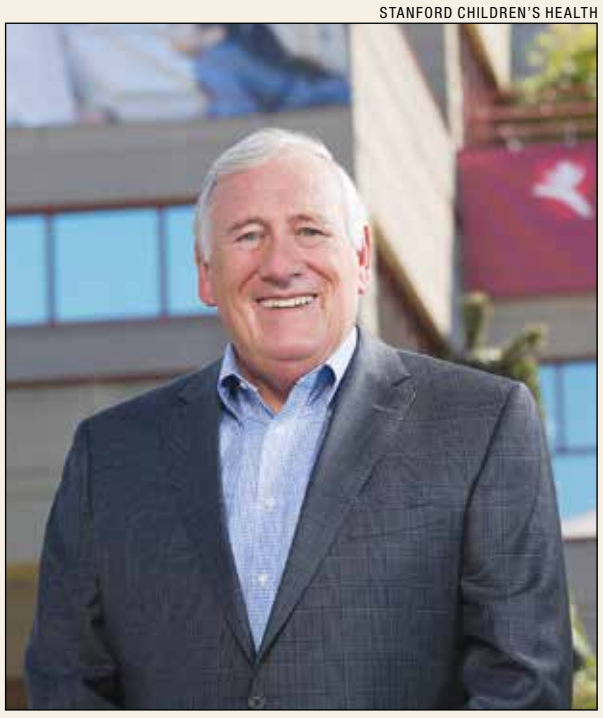
In an open letter to colleagues, Dawes explained that he had planned to announce his retirement a week later, with the intention of continuing in his role until a successor was identified, but that due to recent health developments he would take immediate medical leave.

Twenty-nine years ago, Dawes joined what was then the Children's Hospital at Stanford. He led the opening of Lucile Packard Children's Hospital Stanford in 1991. Eight years later, he was named CEO of the hospital. In the years that followed, Dawes oversaw the hospital's growth of nationally ranked clinical services in areas such as pediatric transplantation, high-risk obstetrics, advanced cancer care and heart surgery, as well as the development of the Stanford Children's Health network. In December 2017, Dawes' efforts culminated with the opening of the new Packard Children's main building — a project he spearheaded for more than a decade.

'A tireless champion of children's health'

"After my 21 years at the helm overseeing milestones such as these, I believe it is now time to pass the baton to the next generation of executives," Dawes said in the letter.

STANFORD CHILDREN'S HEALTH



Christopher Dawes, who oversaw the development of Stanford Medicine's pediatric health network and Lucile Packard Children's Hospital Stanford, announced his retirement on March 20.

He added: "I have been truly honored to serve all the staff and faculty associated with Lucile Packard Children's Hospital Stanford, and Stanford Children's Health, and I am particularly thankful to Susan Packard Orr and the entire Packard family."

Lloyd Minor, MD, dean of the School of Medicine, extended his appreciation to Dawes for his vital contributions to Stanford Medicine. "Chris has been a tireless champion of children's health at Stanford, overseeing the original opening of Lucile Packard Children's Hospital and then — almost two decades later — the completion of the hospital's remarkable new main building," Minor said. "In addition, he helped to bring incredible advances in clinical services to our youngest patients. I am extraordinarily grateful to Chris for his dedication to Stanford and commitment to ensuring better health outcomes for children here in our community and around the world."

Plans for a national search

In the coming months, Jeffrey Chambers, chair of the board of directors at the children's hospital, will lead a national search for a suitable replacement for the organization's president and CEO. Dawes' colleagues are hopeful that he will be able to return at some point to join the process of identifying his successor.

"On behalf of everyone across Stanford Children's Health, we are very supportive of Chris' decision to focus his full energy on his health," Lund said. "As an organization, we will stay the course that Chris has set into motion for continued growth of key programs and expanded access to Stanford Children's Health services. Most importantly, we want to recognize and thank Chris for his nearly 30 years of extraordinary service." **ISM**

OF NOTE

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

SHUCHI ANAND, MD, was appointed assistant professor of medicine, effective Feb. 1. Her research focuses on using practical tools to improve care for patients with kidney disease living in low-resource settings, including India and Sri Lanka.

MAXIMILIAN DIEHN, MD, PhD, was promoted to associate professor of radiation oncology, effective March 1. He focuses on the development and application of liquid biopsy methods for cancer, as well as on understanding and overcoming resistance to cancer treatment.

DITA GRATZINGER, MD, PhD, was promoted to associate professor of pathology, effective Feb. 1. Her research focuses on the architecture of cells in bone marrow and lymph nodes, as well as ways to maximize the diagnostic value of small biopsies to promote rapid, personalized patient care. She is the director of the hematopathology fellowship.

ROBERT HARRINGTON, MD, the Arthur L. Bloomfield Professor of Medicine and chair of the Department of Medicine, was elected president-elect of the American Heart Association. He will be president in 2019-20. He is an interventional cardiologist whose interests include fostering scientific collaborations to conduct clinical research and the evaluation of antithrombotic therapies.

ODETTE HARRIS, MD, was promoted to professor of neurosurgery, effective Feb. 1. Her research focuses on the epidemiology of traumatic brain injury and on characterizing and improving the delivery of neurosurgical services in the developing world and in underserved communities. She serves as Stanford's director of brain injury in the Department of Neurosurgery, which involves managing and coordinating the medical and surgical care for patients with traumatic brain injury.

DESIREE LABEAUD, MD, associate professor of pediatrics, was named the 2018 Women in Science Speaker by the International Society for Antiviral Research. The award recognizes a female scientist who has made outstanding contributions to antiviral and virology science. She will deliver the address, "Making the invisible visible: Arbovirus transmission, risk, disease and prevention in Kenya," in June in Portugal.

JIN BILLY LI, PhD, was promoted to associate professor of genetics, effective Dec. 1. His research focuses on identifying when RNA is edited or modified and understanding the regulation and function of RNA.

WILLIAM H. ROBINSON, MD, was promoted to professor of medicine, effective Feb. 1. His research aims to understand the initiation, natural remission and progression of autoimmune diseases, particularly of rheumatoid arthritis and multiple sclerosis; to elucidate the development of osteoarthritis; and to develop therapeutics for these diseases.

NELSON TENG, MD, was promoted to professor of obstetrics and gynecology, effective Jan. 1. His research interests include new treatment modalities, biologic response modifiers and immunotherapy, in particular a class of naturally occurring human antibodies in the treatment of gynecologic malignancies.

SHERRY WREN, MD, professor of surgery, was elected president of the Pacific Coast Surgical Association for a term beginning in 2021. The association, which represents California, Oregon, Hawaii, Washington and British Columbia, works to advance the science and practice of surgery. **ISM**

Shuchi Anand

Maximilian Diehn

Dita Gratzinger

Robert Harrington

Odette Harris

Desiree LaBeaud

Jin Billy Li

William H. Robinson

Nelson Teng

Sherry Wren

Four faculty members are elected to American Society for Clinical Investigation

Four Stanford Medicine faculty members were elected to the American Society for Clinical Medicine, an honor society of clinician-researchers founded in 1908. They will be inducted in April in Chicago. The society adds fewer than 80 new members each year, and new members must be younger than 50 years old.

The new members from Stanford are:

- Paul Bollyky, MD, PhD, assistant professor of medicine and of microbiology and immunology, who specializes in infectious disease and the immunology of diabetes and diabetic wound management.
- Rajat Rohatgi, MD, PhD, associate professor of biochemistry and of medicine, who investigates the signaling mechanisms that mediate cell-to-cell communication in development, disease and homeostasis.
- Mintu Turakhia, MD, associate professor of medicine, a cardiac electrophysiologist who conducts clinical trials and outcomes research on interventions for heart rhythm disorders, such as atrial fibrillation.
- Robert West, MD, PhD, professor of pathology, who investigates the molecular drivers of tumor formation, particularly in breast cancer and head and neck cancers, with the goal of identifying potential prognostic and therapeutic targets. **ISM**