Graduating med students meet their matches

By Tracie White

Victoria Boggiano, a soon-to-gradu-ate 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, a timer counted down the minutes and seconds until 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

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 garnered 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 the University of California-San Francisco, have pinpointed 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 Har- ris 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

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... gene-editing tool, but it’s not without risk.

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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.

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 50 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 cause Sal had reacted poorly to previous rounds of chemotherapy. Did this mean?

“Prior to CAR-T cell therapy, you would not even use that word, ‘cure,’” Davis said.

“I was very worried,” Davis said. “But there really weren’t any other good options for Sal.” When the 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 is 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,’” 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 Sal 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 breathed 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 in- vetoriate Oakland As 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.

“I 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 leukemia 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 a high-risk group. Sal’s cancer cells harbored a dangerous genetic change known as a Philadelphia chromosome. This mutation is very 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 strongly 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 both harder to detect at an early stage. If caught in its earliest stages, the disease can be treated with surgery or chemotherapy. This is not the case with leukemia, which affects blood and bone marrow. It is possible that the disease may have been present in the body for years before symptoms began.

Instead, cancer cells in children often arise as a result of one or two powerful mutations. These mutations 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 pedi- atries and of medicine, associate director of the Stanford Cancer Institute and di- rector of the Stanford Center for Cancer Cell Therapy.

“A child’s cells, which have tons of de- velopment 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 muta- tions 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 upp a nonexistent im- mune 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 ther- apy,” Mackall said.

“I was working in the field of can- cer immunotherapy for 40 years, and there’s never been a more exciting time,” said immunotherapist pioneer Ronald Levy, MD, professor of medicine and the Robert W. and Helen K. Summy Profes- sor in the School of Medicine. “Some of the responses we’re seeing with this treat- ment are nothing short of miraculous. The world of cancer immunotherapy has changed forever.”

Weighing the costs

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

And although it is costly to remove, genetic engineering at the level of the pa- tient’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 fi- nancial reasons. Scientific advances may drive the cost down, too, as we continue to harness and evolve in the cost of the technology,” Mackall said.

“We did imagine that we would one day have cellphones that don’t do what they do for the amount of money 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 in- fused, his — John Sanford

MARCH 26, 2018 IN THE NEWS

Inside Stanford Medicine is produced by Office of Communication & Public Affairs, Stanford University, School of Medicine 3172 Porter Drive, Palo Alto, CA 94304 Mail code 5471 Phone: 650-723-6891 http://med.stanford.edu/news/ Send letters, comments and story ideas to John Sanford at 723-8309 or at johnsandford@stanford.edu. Please also contact him to receive an e-mail version of Inside Stanford Medicine.
Artificial intelligence is hard at work crunching health data to improve diagnostics and help doctors make decisions for their patients. But researchers at the School of Medicine say the fertile 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 acknowledge 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 to identify patients at risk resides with the 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 raise are:

- Data used to create algorithms can contain bias that can be inherited in the algorithms and in the clinical recommendations they generate. Also, algorithms might be skewed to reflect 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 the algorithms are created, critically assess the sources of 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 treatment outcomes are 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.
- It’s important 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 despite超标 emissions of nitrogen oxide during the tests.

David Magnus, PhD, senior associate dean for the medical humanities and director of the Stanford Center for Bioethical and Social Sciences Institute.

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David Magnus, PhD, senior associate dean for the medical humanities and director of the Stanford Center for Bioethical and Social Sciences Institute.
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 at 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 not just to target and 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 cardiovascu- lar 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 diseases like sickle-cell anemia, AIDS, cancer and heart diseases.”

CRISPR was introduced to the world in 2012, and the technology has since generated a number of patents. Rarely a week goes by without news of another CRISPR “breakthrough.” But the rapid pace of research means little about the regulation and oversight of this gene-altering tool.chner.

CRISPR will be used to design custom 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 bio- ethicist 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 dis- eases 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 instruc- tions 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 bunch of DNA blocks — converted to T in a gene that makes hemoglobin, the protein in red blood cells that deliv- ers oxygen from the lungs to the rest of the body. “It’s like having one typo in a book containing 6 billion letters,” said Mar- thel 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 mutation using older gene-editing technologies, but with CRISPR, we fi- nally had a tool that was much easier to use and far more efficient.” Hemoglobin helps red blood cells maintain a smooth, round shape, which enables them to move freely through blood vessels. But in sickle-cell disease, the damaged gene produces stiff, sticky red cells that clump together into a sickle shape after delivering oxygen. The sick- led cells often clump together, causing extreme pain by blocking the flow of oxygen-rich, normal red blood cells to vital organs.

For David Sanchez, prolonged blockages led to chronic kidney disease and permanent damage to his spleen. By age 10, he had been admitted to Pack- ard Children’s Hospital with a heart attack and chest pains. Since then, he has lived with sickle-cell anemia, a condition that occurs when sickled cells block the flow of oxygen to the lungs and other organs.

“The hospital is my second home. I always have good doctors here,” said Da- vid, who has also experienced back pain so severe he could barely walk. “He’s been poking and prodding since infancy,” said Dolores Sanchez, David’s grand- mother and legal guardian.

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

Sickle-cell disease affects about 100,000 people in the United States, pri- marily African-Americans, and millions worldwide. About 15 percent of patients can be cured with a bone-marrow transplant from a healthy sibling. “Every year 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. It’s a gift from Mother Nature,” said Stanley Qi, PhD, an assis- tant professor of bioengineering and of chemical and systems biology, and the scientific co-founder and advisory board member of Refuge Biotherapeutics Inc., which uses CRISPR technol- ogy. “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 seg- ments of DNA in other microbial spe- cies. 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 cut DNA. Scientists eventually realized that bacteria have been using CRISPR-Cas complexes for billions of years to fight off and destroy enemy viruses, and that this ancient bac- terial immune system could be adapted for use in genetic engineering. In 2012, allergic predator professor Jennifer Doudna, PhD, and her colleagues showed how CRISPR and the enzyme Cas9 could be used to engineer a virus to find and cut specific sequences of DNA in a test tube. The following year, separate stud- ies by Madeline and Doudna — including the MIT team led by Stanford alumnus Feng Zhang, PhD — demonstrated that Cas9 and CRISPR could be programmed to edit human DNA.

“These landmark studies demonstra- ted 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 a RNA mol- ecule that anneals to the DNA sequence in that gene. You then combine the RNA with a Cas9 enzyme, which can cut the DNA at exactly the same sites.”

The RNA acts like a very fast GPS — it guides the Cas9 enzyme to the mutated DNA sequence. The enzyme then binds to the RNA, cuts the DNA and repairs the damage.

The final repair can be done using a benign virus that engineers to deliver another DNA edit, known as a CRISPR-Cas9 genome.”

Older gene-editing tools use proteins instead of RNA to target damaged genes. But it can take months to design a sin- gle, 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 is disposable, so it 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 who have sickle cell disease have two defective hemoglobin genes in their stem cells, one from each parent. To- gether, 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. But normal 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 pa- tients with sickle-cell disease. The idea is to transform the patients into healthy people with sickle-cell trait by creating their defective stem cells with two abnor- mal hemoglobin genes in stem cells with one normal gene. This so-called 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 en- gineer a virus to deliver the correct se- quence 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 chemo- therapy to create a space in the patient’s bone marrow where the new stem cells can be taken up,” Porteus said. “The repaired stem cells could create enough normal red blood cells for the patient to have a normal life span.”

“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 the disease is only triggered when a certain proportion of sickle cells occur. It’s not a threshold that occurs only if the proportion of sick- led cells in the bloodstream is above 30 percent. As long as 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
CRISPR is a gift from Mother Nature.

Designer babies

Clinical trials of CRISPR like the one Porteus is proposing have broad public support, in part because using CRISPR in sickle-cell patients makes clinical sense. The DNA, but not that of their offspring. Editing human embryos to repair disease-causing genes is far more controversial. One concern is that CRISPR could be used to make designer babies, which is part of a three-hour procedure known as spheresis, in which David's diseased red blood cells are removed and replaced with normal donor 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.

David recovered from the surgery and has enrolled as a junior at Stanford 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.

"It's quite possible that people who are well-dosed with CRISPR to cure sickle-cell disease 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.

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 type that causes sickle-cell disease.

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Greely compared the invention of CRISPR to a "gene editing as one of the four biggest promises, the others being clean water, cheap energy, and better medicine.

"It requires manipulating lots of different systems at the same time, especially the immune system, which is not fully predictable," Greely added.

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 effects. And we do all the manipulations in 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.

"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 illegal for CRISPR to be misused accidentally or intentionally.

"The Obama administration listed gene editing as one of the four biggest promises, the others being clean water, cheap energy, and better medicine.

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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 forum, “Gun Violence and Public Health: What We Know,” in conjunction with the ASK campaign, in which parents ask anyone who might be supervising children about gun safety or storing poisons, “Firearm counseling should be nonambiguous and nonjudgmental, Sandberg said. "Firearm counseling is a role to play in that changing of hearts and minds."" 

MARCH 26, 2018 INSIDE STANFORD MEDICINE
Skeleton continued from page 1

was published online March 22 in Ge-
nome Research. Sanchita Bhattacharya, a 
bioinformatics researcher at UCSC, 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 Des- 
cert of Chile. After trading hands and 
eventually finding a permanent home in 
Spain, the mummified specimen started 
to attract attention. Ata is estimated to 
be about 6 inches tall — about the length of 
dollar bill — with an angular, elongated 
skull and sunken, slanted eye sockets, 
the internet began to bubble with other-
worldly hullabaloo and talk of ET.

Over the years, Ata's story about a 
through a friend of mine, and I 
and not think it's interesting; it's 
completely different. So I told my 
friend, 'Look, whatever it is, if 
it's got DNA, I can do the 
analysis.'"

In addition, Nolan said that Ata 
likely a fetus, that had suffered severe 
genetic mutations. Ata's genome 
showed the same in the young and old cells,” said Brunet.

The genomic results confirmed Ata's 
Chilean descent and turned up a list of 
mutations in seven genes that separately or in combination to various bone deformities, facial malformations or skeletal dysplasia, more commonly

Proteins continued from page 1

less proficient at disposing of these protein aggregates, and their ability to respond readily to "make new neu-
rons" 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 process of protein production and disposal throughout the life 
and activation status of neural stem cells.

"We were surprised by this finding because resting- 
or quiescent, neural stem cells have thought to be a 
really pristine cell type just waiting for activation," said Anne Brunet, PhD, professor of genetics. "But now that we have today to really see what 
interesting exercise in applying the tools 
that we have today to really see what 
we could find," he said. "The pheno-
type, the symptoms and size of this girl 
were extremely unusual, and analyz-
tions 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 
step investigating when we find one 
gene that might explain a symptom. It 
seems like a really simple thing going 
wrong, and it's worth getting a full 
explanation, especially as we head closer 
and closer to gene therapy," Brunet 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 Sock-
ell; senior research scientist Felice Bava, PhD, and Carlos Bustamante, PhD, pr-
ofessor of biomedical data science and of genetics.

Researchers at UCSC, Roche Sequenc-
ing Solutions, National Autonomous 
University of Mexico and Ultra Intel-
ligence Corporation also contributed to 
the work. Nolan is a member of Stanford Bio-X, the 
Stanford Child Health Research Insti-
tute and the Stanford Cancer Institute. 

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Human Frontier Science Program. 

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

"We’d like to know whether the aggregated proteins 
are the same in the young and old cells," said Brunet. 

“Wat do they do? Are they good or bad? Are they stor-
ing factors important for activation? If so, can we 
help elderly resting stem cells activate more quickly by bar-
ketting these factors? Their existence in young cells 
suggests they may be serving an important function.”

Other Stanford authors are former postdoctoral 
scholars Katja Hesbert, PhD, and Ashley Webb, PhD; 
postdoctoral scholars Tyson Ruetz, PhD, Salah Mah-
moudi, PhD, and Xiaoxi Zhao, MD, PhD; graduate 
students Andrew McKay, Robin Yeo and Ben Dulken; 
former graduate student Elizabeth Pollina, PhD; lab-
atory 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 Insti-
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ing Graduate Fellowship and a Stanford cancer biology 
training grant.

Stanford's Department of Genetics also supported the work.

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

Old resting stem cells, Leeman found, express fewer 
lysosom-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 
resting cells or subjecting them to starvation 
conditions to limit their protein production actually 
restored the ability of these older resting 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 proteases over lysos-
omes and to determine how the regulation of protein 
aggregation becomes disrupted during aging.

"Are they good or bad?"

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Alberto Bassan, postdoctoral scholar at UCSC, is one of 
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ing Graduate Fellowship and a Stanford cancer biology 
training grant.
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. 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 our 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.”

Four faculty members are elected to American Society for Clinical Investigation

Four Stanford Medicine faculty members were elected to the American Society for Clinical Investigation, 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.

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 2020-2021. 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 autoantibodies; 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.

Christopher Dawes, CEO of Stanford Children’s Health.