INSIDE STANFORD MEDICINE

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Paul King has been named the new president and CEO of Stanford Children's Health.

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Study: Anti-CD47 cancer therapy appears safe

By Christopher Vaughan and Krista Conger

A novel immunotherapy appears safe for use in patients with a type of blood cancer called non-Hodgkin's lymphoma, according to a phase-1 multicenter clinical trial led by a researcher at the School of Medicine.

Although some patients showed signs of transitory anemia or reactions at the injection site, there were few other significant side effects to the treatment, the researchers said.

The therapy combines an experimental antibody developed by researchers at Stanford and a commercially available anti-cancer antibody called rituximab. The experimental antibody, known as Hu5F9-G4, blocks the protein CD47, a "don't eat me" signal that inhibits immune attacks on cancer cells. The antibody combination was used to treat people with two types of non-Hodgkin's lymphoma: diffuse large B-cell lymphoma and follicular lymphoma.

Half of the 22 people enrolled in phase 1 of the trial had a positive response to the therapy, and about one-third went into complete remission from their cancer.

"It was very gratifying to see how the treatment was well-tolerated and showed a clinically meaningful response," said Ranjana Advani, MD, professor of medicine at Stanford.

A paper describing the results of the phase-1 trial was published Nov. 1 in *The New England Journal of Medicine*. Advani is the lead author. The senior author is Sonali Smith, MD, a professor of medicine at the University of Chicago.

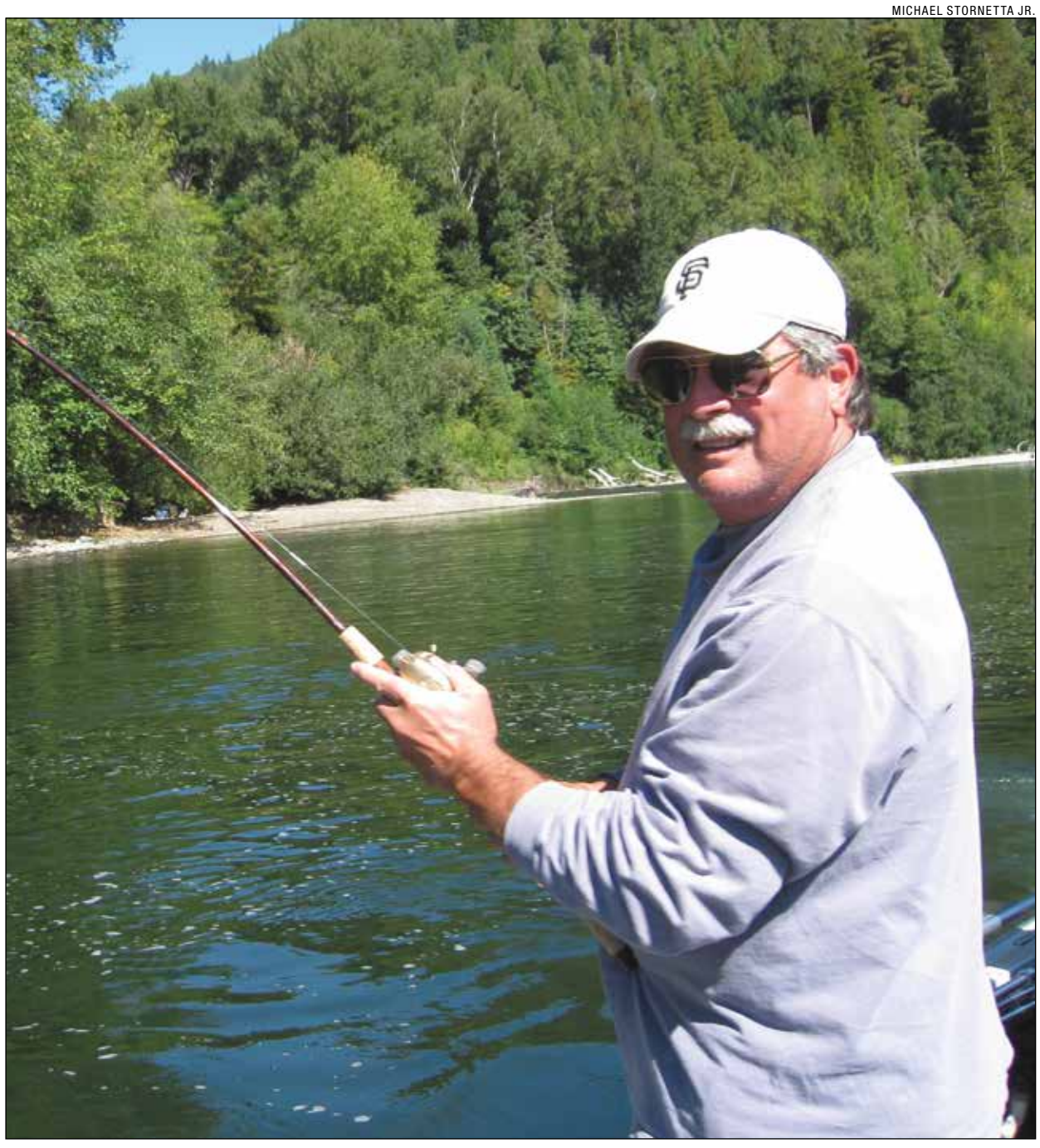
The trial was funded by Forty Seven Inc., the company that licensed the patent from Stanford to produce Hu5F9-G4, and by the Leukemia and Lymphoma Society.

Silencing 'don't eat me' signal

In 2010, researchers led by Irving Weissman, MD, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, showed that nearly all cancer cells cover themselves with a protein known as CD47, which acts as a "don't eat me" signal to immune cells called macrophages.

Weissman and his colleagues later developed an antibody called Hu5F9-G4 that blocks the CD47 protein, prompting macrophages to engulf and devour cancer cells. Rituximab is an antibody that has been shown to amplify positive "eat me" signals. See CD47, page 6

MICHAEL STORNETTA JR.



Michael Stornetta, who is being treated for cancer, participated in a clinical trial testing the safety of a therapy that combines an experimental antibody developed at Stanford and a commercially available antibody. Scans showed his cancer was significantly reduced.

Heart study enrolls more than 400,000 people

By Tracie White

A clinical trial to determine whether a smartwatch app that analyzes pulse-rate data can screen for a heart-rhythm disorder has enrolled more than 400,000 participants.

Researchers at Stanford Medicine, in collaboration with Apple, launched the Apple Heart Study last November to determine whether a mobile app that uses the optical sensor on the Apple Watch to analyze pulse rate data can identify atrial fibrillation. The condition, which is characterized by an irregular heartbeat, often remains hidden because many people don't experience symptoms. Atrial fibrillation can increase the risk of stroke and heart failure.

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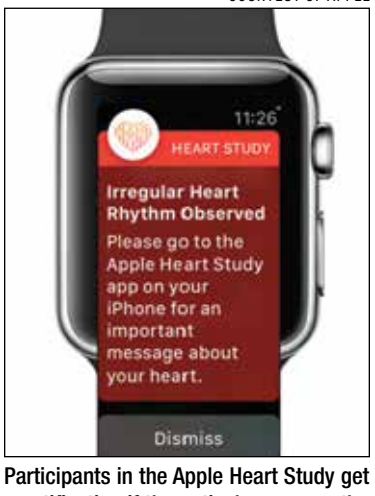


Participants in the Apple Heart Study get a notification if the optical sensor on the Apple Watch detects an irregular pulse.

A paper describing the design of this unique clinical trial, the largest screening study on atrial fibrillation ever done, was published online Nov. 1 in the *American Heart Journal*. Enrollment, which was conducted through an iPhone app, is now closed.

The study has entered the final phase of data collection and will be completed early next year, the researchers said. The Stanford team is led by principal investigators Mintu Turakhia, MD, associate professor of cardiovascular medicine, and Marco Perez, MD, assistant professor of cardiovascular medicine, and by study chair Kenneth Mahaffey, MD, professor of cardiovascular medicine.

"We hope this study will help us better understand how wearable technologies can inform precision health," said Lloyd Minor, MD, dean of the School of Medicine. "These new tools, which have the potential to predict, prevent and manage disease, are finally within our reach."

The Food and Drug Administration announced Sept. 11 that it had cleared two mobile medical apps designed by Apple to work on the Apple Watch. One app uses data from new hardware on the Apple Watch Series 4 to take an electrocardiogram by touching the button on the side of the device. The other app uses data from an optical sensor available on the Apple Watch Series 1 and later to analyze pulse data to identify irregular heart rhythms suggestive of atrial fibrillation and notify the user. The Apple Heart Study involves only See APPLE, page 7

Secret behind Bambi's fast-growing antlers revealed in research

By Hanae Armitage

Each spring, male deer sprout a new pair of antlers, which are essentially temporary external bones, at a speed unparalleled by the bone growth of other mammals. Now, research led by scientists at the School of Medicine has identi- See ANTLER, page 6

VLAD SOKOLOVSKY/SHUTTERSTOCK.COM

Deer antlers are essentially regenerating bone. During the spring, they begin to sprout, and by winter, they start to shed.

Three are awarded the School of Medicine's highest honor

By Julie Greicius

One illuminated key principles in brain development. Another enabled new hope for detecting cancer at its earliest stages. And another volunteered years of his time to advance the cause of Stanford Medicine.

Together, they are the 2018 recipients of the highest honor bestowed by the School of Medicine, the Dean's Medal, which is presented to individuals whose contributions have significantly advanced the mission of Stanford Medicine.

Carla Shatz

Don Listwin

Ron Johnson

The recipients are Carla Shatz, PhD, the Sapp Family Provostial Professor, the David Starr Jordan Director of Stanford Bio-X and a professor of biology and of neurobiology; Don Listwin, founder and chairman of the Canary Foundation, which supports programs for early cancer detection; and Ron Johnson, founder and CEO of Enjoy, a company that hand-delivers technology products and helps customers set them up.

"The collaborative effort to advance the biomedical revolution in precision health takes many forms," said Lloyd Minor, MD, dean of the School of Medicine. "This year's medal recipients have used their passions for science, philanthropy and service to help bring about exceptional progress in research and clinical care. I'm proud to honor their work."

Improving brain plasticity

Shatz's interest in the brain's visual system began as an undergraduate at Radcliffe College. She went on to study how the eye and brain connect during development, and her lab discovered that, in the earliest stages before the eye can even see, it sends coordinated test patterns of neural activity to the brain. Those test patterns develop the brain circuits needed for vision to emerge from immature circuits; in other words, as Shatz wrote in 1992, "Neurons that fire together, wire together."

Shatz has gone on to discover that this early neural signaling, which is needed for synapse plasticity and pruning, involves interactions common to both the brain and immune systems. Her discoveries have implications for improving brain plasticity and memory, and for treating neurological disorders such as schizophrenia to Alzheimer's disease. The Dean's Medal recognizes Shatz's groundbreaking research and impact on our understanding of neural development.

"It's an immense honor to be recognized with the Dean's Medal," Shatz said. "I want to recognize and thank the incredible students and postdocs in my lab. Without them, none of our discoveries would have happened. What's more, it is a great privilege to be involved in Stanford Bio-X, where transforming, high-risk ideas emanating at the crossroads of disciplines are encouraged."

Earliest cancer detection

Living through his mother's death from ovarian cancer left an indelible mark on Listwin and inspired him to work toward progress in early cancer detection. Listwin's role in helping to create today's global internet infrastructure through multibillion-dollar technology investing and management, including a decade at Cisco Systems, enabled him to step back from his operating roles to build the Canary Foundation.

Today, 15 years later, the Canary Foundation has grown from a startup nonprofit to a leader in the development of early cancer detection programs, including the Canary Center at Stanford and many others in the United States and abroad. The Canary Foundation is the only nonprofit exclusively dedicated to research in the field of early detection of cancer. The Dean's Medal honors Listwin for his service in the scientific and philanthropic communities that have advanced precision health.

"My thanks to Dean Minor and the entire School of Medicine organization," Listwin said. "Over the past decade, a theme of partnership has emerged in my pursuits in the medical field, and none has been stronger than at Stanford. Whether working with Dr. Sam Gambhir to build the first comprehensive early cancer detection center or launching a modest vision clinic in Belize with Dr. Caroline Fisher, there has always been support from the School of Medicine. My current pursuit in the field of stroke also found it roots at Stanford. It is a privilege to be able to engage in a spectrum of work in the field of medicine with the best in the world to help solve these critical problems."

Designing the ideal hospital

Known as the executive team member at Apple who founded its stores and helped create a unique user experience for its customers, Johnson had also transformed merchandising at Target through a focus on design. Johnson now leads Enjoy Technology Inc. He's been a Stanford volunteer for many years and is currently on the university's Board of Trustees.

Johnson was on the Stanford Health Care board for nine years and served as co-chair of the campaign for Stanford Medicine. He conceived of and led the Stanford Medicine Corporate Partners program, which raised nearly 50 percent of the funds for the new Stanford Hospital. In addition, Johnson brought his expertise in retail design to bear on the design of the new hospital, helping to shape a patient-centered care setting that would be welcoming and easy to navigate.

The Dean's Medal recognizes Johnson's years of dedicated service to Stanford Medicine and his influence on its future.

"Volunteering for Stanford Medicine over the past decade has been a gift," Johnson said. "The opportunity to work with such incredibly talented people to deliver on our vision of precision health has been among the most gratifying experiences of my life. The new Stanford Hospital will be a symbol of excellence for Stanford for decades to come." **ISM**

Study identifies link between DNA-protein binding, cancer onset

By Helen Santoro

Researchers at the School of Medicine and their collaborators at other institutions have identified a link between how proteins bind to our DNA and how cancer develops. This finding may allow researchers to predict cancer pathways and long-term patient outcomes.

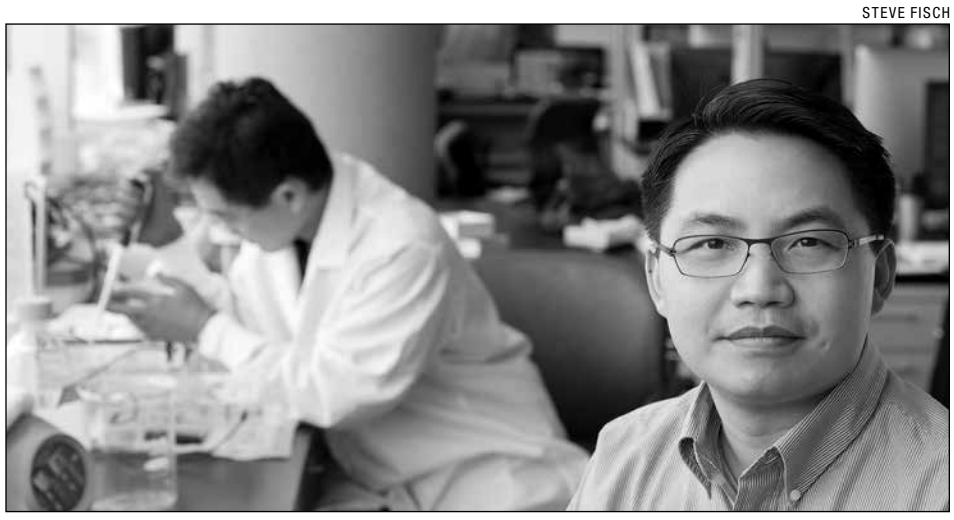
The research focuses on chromatin, the DNA-protein complex where all genes reside. Specifically, it evaluates chromatin's relationship to transcription factors — proteins that play a crucial role in managing which genes are activated within cells. Certain genes are turned on or off based on how transcription factors bind to specific parts of the chromatin. The study found that these binding patterns and the resulting gene activation act like a key to different cancer types, allowing the researchers to understand the biology of cancer at its most basic level.

A paper detailing the research was published Oct. 26 in *Science*. The senior authors are Howard Chang, MD, PhD, professor of dermatology and of genetics, and William Greenleaf, PhD, associate professor of genetics. Postdoctoral scholar Ryan Corces, PhD, and graduate student Jeffrey Granja share lead authorship.

Cancer causes a massive burden on society and is among the leading causes of death worldwide. According to the National Cancer Institute, there will be more than 1.7 million new cancer cases by the end of 2018 in the United States. Our total health care expenditures for cancer care in 2014 alone was $87.8 billion — a number that continues to increase as the years go by.

However, diseases that once seemed intractable now have functional treatments, said Chang, who is also the Virginia and D.K. Ludwig Professor of Cancer Genomics. "So, with continued work, cancer is something we can actually make sense of," he added.

STEVE FISCH



Howard Chang and his colleagues believe their research into "noncoding" DNA will be useful in the development of better cancer prognostics and new treatments that are more localized and effective.

A disease of genes gone awry

Corces said that cancer is "a disease of genes gone awry." But in order to understand where these harmful genes come from, the researchers had to look inside the nucleus to the cell's transcription process.

Transcription occurs when the cell takes information encoded in a gene and rewrites it in the form of messenger RNA. The DNA within a cell's nucleus is tightly wound together with certain proteins into a threadlike structure known as chromatin, and that chromatin is further coiled to form a larger structure called a chromosome. Because of this coiling, only certain areas of the chromatin sequence are accessible to the cell's transcription machinery. When a transcription factor finds an available section of chromatin and binds to it, that region of the DNA sequence unzips, allowing transcription to occur. However, in the case of cancer, the transcription process malfunctions, resulting in a change in gene activation.

To understand exactly what goes wrong during this critical stage, the researchers used 410 tumor samples, representing 23 different cancer types, from the Cancer Genome Atlas and a newly developed technique called assay for transposase-accessible chromatin using sequencing, or ATAC-seq. As Chang explained, ATAC-seq is like spray-painting your DNA but only the accessible chromatin gets painted, giving researchers a fast and easy way to identify key protein-binding areas.

One finding showed that mutations can occur within the chromatin sequence, thereby **See CHROMATIN, page 3**

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STANFORD MEDICINE

Skeletal stem cells revert to primitive state to fix major damage

By Krista Conger

Adult mouse skeletal stem cells in the jaw revert to a more developmentally flexible state when called upon to regenerate large portions of bone and tissue, according to a study by researchers at the School of Medicine.

The finding is the first to show that mammalian adult stem cells can march backward along the developmental timeline in a process called de-differentiation to become more primitive in response to environmental signals. In particular, the cells appeared to regress to a cell type that normally occurs within weeks of conception in humans and that give rise to the bones, cartilage and connective tissue of the head and face.

The results suggest the possibility of using naturally occurring adult stem cells, which are usually restricted to generate only a limited panel of closely related progeny, to carry out more extensive regeneration projects throughout the body — much in the way that salamanders or newts can replace entire limbs or tails.

"It's pretty remarkable that this would happen in an adult animal," said Michael Longaker, MD, professor of plastic and reconstructive surgery. "It changes the way we look at skeletal development and regeneration."

A paper describing the research was published online Oct. 24 in *Nature*. Longaker, the Deane P. and Louise Mitchell Professor in the School of Medicine and co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, shares senior authorship with Howard Chang, MD, PhD, professor of dermatology and of genetics and director of Stanford's Center for Personal Dynamic Regulomes. Graduate students Ava Carter and Ryan Ransom are the lead authors.

Aiding stunted bones

The researchers were studying a common surgical technique called distraction osteogenesis, which is often used in newborns or infants to lengthen abnormally stunted bones in the lower jaw. These malformations occur in conditions such as Pierre-Robin sequence, Treacher Collins syndrome and craniofacial microsomia.

During distraction osteogenesis, the bone is surgically fractured, and an adjustable device is inserted to gradually increase the distance between the ends of the bone over the course of weeks. This encourages new bone growth to fill in the gap and create what resembles a normally developed mandible.

"This is a very special system of regeneration that echoes what normally happens in development," said Chang, who is the Virginia and D.K. Ludwig Professor of Cancer Genomics and a Howard Hughes Medical Institute investigator. "If you cut the bone, and stretch it, you get more bone. But this regeneration requires mechanical force. We wanted to know how skeletal stem cells respond to this kind of environmental signal."

Recently, Stanford researchers identified the skeletal stem cell in both mice and humans. Like other stem cells that occur in adult animals, skeletal stem cells are restricted in their ability to generate different cell types. In particular, they can generate bone, cartilage and stroma (the bone's spongy interior) to repair normal damage like fractures. But the regeneration required by distraction osteogenesis, in which the bone ends are repeatedly moved further apart, is much more extensive.

"How do they know to reform a mandible with the correct shape and function?" said Longaker. "Are they simply recapitulating normal development? And, if so, how?"

Tracking cellular reversion

Carter and Ransom used a technique developed in the Chang laboratory called ATAC-seq to identify gene switches that are turned on in mouse skeletal stem cells in response to the mechanical force of distraction. They found that the cells began to express genes normally found in cranial neural crest cells — cells that arise in humans about five to six weeks after conception and that form the bones, cartilage and connective tissue of the head and face. At the same time, the cells tamped down the expression of genes involved in normal fracture repair.

This was really a surprise," Longaker said. "These cells appear to revert back to a cell type responsible for forming the jaw during early development. That's why the regenerated mandible looks like one formed in early embryogenesis."

DANIEL BRASLAVSKY

Michael Longaker, Ava Carter and Howard Chang are co-authors of a study in which skeletal stem cells in the jaws of adult mice were found to regress to a more primitive state under certain conditions.

In the absence of mechanical force to separate the bone, the skeletal stem cells repaired the fracture without expressing cranial neural crest genes.

Further research identified the focal adhesion kinase molecular pathway as a key player in the ability of the skeletal stem cells to detect and respond to mechanical force. Inhibiting this pathway abolished the ability of the cells to make new bone during distraction osteogenesis.

The finding has provocative clinical implications, the researchers believe.

"Now that we've identified one of the molecular pathways responsible for this developmental shift, it may be possible to target the proteins in that pathway to achieve a similar outcome without the requirement for physical force," Carter said.

"We're beginning to understand in detail how skeletal stem cells are likely to respond to environmental cues in humans," Longaker said. "This is an opportunity to change how we think about the development of not just the skeleton, but also other tissues and organs. Can we go back in time after an organ is formed to trigger more extensive regeneration? This at least opens the door to that possibility."

Longaker is a member of the Stanford Child Health Research Institute, the Stanford Cardiovascular Institute, the Stanford Cancer Institute and Stanford Bio-X. Chang is a member of the Stanford Child Health Research Institute, the Stanford Cancer Institute, the Stanford Neurosciences Institute, Stanford ChEM-H and Stanford Bio-X.

Other Stanford authors are research assistant Ankit Salhotra; former research associate Tripp Leavitt, MD; medical student Owen Marecic; CIRM scholar Michael Lopez; postdoctoral scholars Matthew P. Murphy, MD, Yuning Wei, PhD, and Ruth Ellen Jones, MD; surgical resident Clement Marshall, MD; undergraduate student Ethan Shen; assistant professor of surgery Charles K.F. Chan, PhD; and associate professor of surgery Derrik Wan, MD.

The research was supported by the National Institutes of Health, the HHMI, the Stanford Child Health Research Institute, the Hagey Laboratory for Pediatric Regenerative Medicine, a Steinhart/Reed Award, the Gunn-Oliver Fund and the Scleroderma Research Foundation.

Stanford's departments of Surgery and of Dermatology also supported the work. ISM

Chromatin

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creating a new and accessible site where a transcription factor can bind. Once the protein attaches to the site, a new gene is expressed, causing significant biological changes.

An example of this occurred with bladder cancer tissue that the researchers examined. When the team performed ATAC-seq on the tissue, they noticed that a chromatin mutation created a new protein-binding site that was associated with a strong increase in the activity of a neighboring gene that regulates cell size, motility and shape — all of which are classic factors in cancer growth. Even more interesting was that this particular mutation was not present in the other cancer tissues analyzed in the study, suggesting that different cancer types may arise from different chromatin mutations.

"These switches that determine gene activity were our missing component," Chang said. "We can now find how these switches are changing cancer, including mutations that make the switch get stuck in the on position."

The tip of the iceberg

The vast amount of genetic research is focused on the 2 percent of our DNA that is used to create proteins. In the current study, Chang wanted to explore the other 98 percent. Called the "noncoding" section, this part of our DNA is used to make crucial regulatory components that control gene behavior and activation. It also includes information that is pertinent to cancer.

Through this work, Chang hopes to open the door to understanding the breadth of the human genome, and of cancer itself. Moving forward, the team expects far more research aimed at discovering and understanding the effects of these noncoding sequences.

Although the team's findings have yet to be applied in a clinical setting, the researchers believe their work will be useful in the development of better cancer prognostics, more information on patient susceptibility to cancer and new treatments that are more localized and effective.

Beyond its potential clinical impact, Corces said he believes the research provides valuable knowledge about cancer gene regulation. "Other people are undoubtedly going to use this chromatin accessibility data to further understand how networks of genes effect cancer," he said.

Other Stanford co-authors of the paper are postdoctoral scholar Seung Woo Cho, PhD; graduate student Maxwell Mumbach; research associate Shadi Shams; technician Bryan Louie; research scientists Jose Seoane, PhD, and Ansuman Satpathy, PhD; and assistant professor Christina Curtis, PhD.

Researchers from several other institutions were co-authors of the work and are listed in the paper.

Chang is a Howard Hughes Medical Institute investigator, and Greenleaf is a Chan-Zuckerberg Biohub investigator. They are both members of Stanford Bio-X, the Stanford Cancer Institute, the Stanford Neurosciences Institute and the Stanford Child Health Research Institute.

The research was supported by the National Institutes of Health and the Parker Institute for Cancer Immunotherapy.

Stanford's departments of Genetics and of Dermatology also supported this work. ISM

Researchers awarded nearly $5 million to map cells of colon

Scientists at the School of Medicine will launch a center to map the mosaic of cells that comprise the human colon.

Michael Snyder, PhD, professor and chair of genetics, and Gary Nolan, PhD, professor of microbiology and immunology, will lead the Stanford Tissue Mapping Center, which is being funded by $4.9 million from the National Institutes of Health.

In addition to mapping the types of cells that make up colon tissue, the center aims to reveal the spatial organization of the cells, with the intention of providing insights into how cell types and their locations contribute to the function of the colon. Through the center, the scientists also aim to understand and treat many intestinal and colorectal diseases, such as inflammatory bowel disease, ulcerative colitis and colon cancer.

The research will contribute to the Human Biomolecular Atlas Program, a larger effort supported by the NIH to map the entire human body at the level of individual cells. ISM

Heart recipient: 'Stanford has saved my life not once, but twice'

By Grace Hammerstrom

Today, Yolanda Ishaq's "miracle baby" is 25 years old, and Ishaq herself is a grandmother. She continues to thrive after receiving a second heart transplant and a kidney transplant at Stanford Hospital in 2015.

"Stanford has saved my life not once, but twice," said Ishaq, who lives in Oakland, California. "They've also given my daughter life. It was unheard of to have a baby back then after a heart transplant."

Ishaq's story began about two decades after Norman Shumway, MD, PhD, a cardiothoracic surgeon at Stanford, performed the first successful adult human heart transplant in the United States in 1968. In the 50 years since that historic operation, heart transplantation continues to be one of the few treatment options available for end-stage heart disease.

"Heart transplantation opened up a potential life-saving treatment for people who were dying of heart disease," said Sharon Hunt, MD, PhD, a professor emerita of medicine who was a Stanford medical student when Shumway performed his first transplant. She later became Ishaq's transplant cardiologist.

Life was 'literally hell'

For Ishaq, a nagging cold was the first sign that something was wrong. After multiple trips to the doctor she was diagnosed with an enlarged heart. It could no longer pump blood effectively to her body. She went from working full-time and enjoying life to barely being able to walk from one room to another without getting out of breath.

"Life before my first heart transplant was literally hell," she said. "I couldn't function as a person on a day-to-day basis with the heart that I had." When medical therapy failed to improve her condition, Ishaq's doctor referred her to Stanford. At her first appointment, she knew she was in the right place.

Her Stanford cardiology team continued to monitor her enlarged heart, and placed her on the transplant list when it was clear that her right side had completely failed, and her left side was on its way to failing. "I believed they would make me better," she said. "I love my entire transplant team. Without them, I would not be here."

She underwent a heart transplant in 1991 and, when she became pregnant a year later, she asked Hunt, "Can I keep it?" At the time, the Stanford transplant team discouraged heart recipients from conceiving a child because of the risk of complications to the organ, such as rejection, infection and graft dysfunction, a life-threatening complication that affects the heart's ability to circulate blood effectively. But Ishaq was willing to do whatever it would take to have a baby, and Hunt was ready to help.

"That's how I had my daughter Monique," Ishaq said. "She is the first baby born to a heart transplant recipient at Stanford. The delivery room was packed with 28 people, all of whom wanted to witness the historic birth."

Ishaq was fine for 24 years with her new heart, and Hunt continued to care for her. But she had a setback in mid-2015 when her heart and kidneys began to fail. Her blood pressure periodically plummeted, causing fainting spells. The first time it occurred, it was the middle of the night. Ishaq woke up on the floor, her dog persistently nudging and licking her. His bark alerted her daughter that something was wrong, and Ishaq was rushed to Stanford Hospital. "He is my furry savior," Ishaq said of her dog.

STEVE FISCH

Yolanda Ishaq (left), who received two heart transplants and a kidney transplant at Stanford Hospital, with her daughter Monique Crawford and grandson Jonah, who were both born at Stanford.

Ishaq experienced three more of these episodes, and three more trips to the hospital. In July of that year, her Stanford cardiologist adjusted her pacemaker to stabilize her condition until a second donor heart became available.

Ishaq received a second heart transplant on Nov. 9, 2015. Because her body was also showing signs of kidney failure, her Stanford transplant team decided to simultaneously conduct a kidney transplant.

Stanford at 'heart' of innovation

Today, approximately 50 patients undergo heart transplantation at Stanford each year, and the program has performed more than 1,200 heart transplants over five decades. Stanford remains the oldest, continuously operating heart transplant center in the world, and its physicians are responsible for many of the innovations that continue to improve long-term survival.

Research conducted by Shumway and his team led to the use of the antirejection drug cyclosporine and to an innovative biopsy technique that allows doctors to spot rejection in a transplanted organ even earlier and administer antirejection measures to save the heart.

Stanford doctors also performed the first successful simultaneous transplant of the heart and lungs, and the first successful implantation of a left ventricular assist device, which is a mechanical pump that helps weakened hearts continue to circulate blood. Additional Stanford contributions to the field include the creation of the classification system used to determine rejection, and the development of a noninvasive way to detect rejection earlier than previously possible.

"Stanford really is the birthplace of heart transplantation," said Kiran Khush, MD, associate professor of medicine at the Stanford School of Medicine and a transplant cardiologist who works as part of a team of physicians, nurses, physical therapists, social workers, dieticians and pharmacists to care for patients before, during and after heart transplantation at Stanford Hospital.

For Ishaq's daughter Monique Crawford, Stanford is simply home. "It's where my son Jonah was born. It's where I was born," she said. "And it's where my mom got both of her new lives. Stanford is definitely a special place for us." ISM

'DNA origami' triggers tissue generation in early development

By Krista Conger

A developing embryo faces the difficult task of concocting myriad tissue types — including skin, bone and the specialized glop that makes up our internal organs and immune system — from essentially the same set of ingredients: immature, seemingly directionless stem cells. Although some of the important players that provide direction to this transformation are known, it's not been clear exactly how they work together to accomplish this feat.

Now, researchers at the School of Medicine have identified a key regulatory hierarchy in which proteins called morphogens control gene expression by directing the looping of DNA in a cell. This looping brings master regulators called transcription factors in contact with specific sets of genes necessary to make particular tissue types.

Varying concentrations and types of morphogens cause different looping events, directing different cell fates much in the same way that railroad workers control the direction and eventual destination of a train car by connecting different portions of track.

Although the researchers were particularly interested in learning more about how to stimulate the production of a type of skin cell called keratinocytes to treat epidermolysis bullosa, a blistering skin disease with few treatments, they believe their findings may have implications for the derivation of other therapeutically useful tissue types.

"For the first time, we were able to see how morphogens and master transcriptional regulators work together to make specific cell types," said Anthony Oro, MD, PhD, professor of dermatology. "We've always wondered how a transcription factor required for the production of vastly different cell types knows which genes to make into proteins in which situation. Now we've answered that question: morphogens help the master transcription factors hook up to the right targets. Changing the concentration or type of morphogen, or even the order in which they are added to a cell, causes dramatically different outcomes."

A paper describing the research was published online Nov. 5 in *Nature Genetics*.

Oro, who is also the Eugene and Gloria Bauer Professor, is the senior author. Postdoctoral scholar Jillian Pattison, PhD; former postdoctoral scholar Sandra Melo, PhD; and graduate student Samantha Piekos share lead authorship.

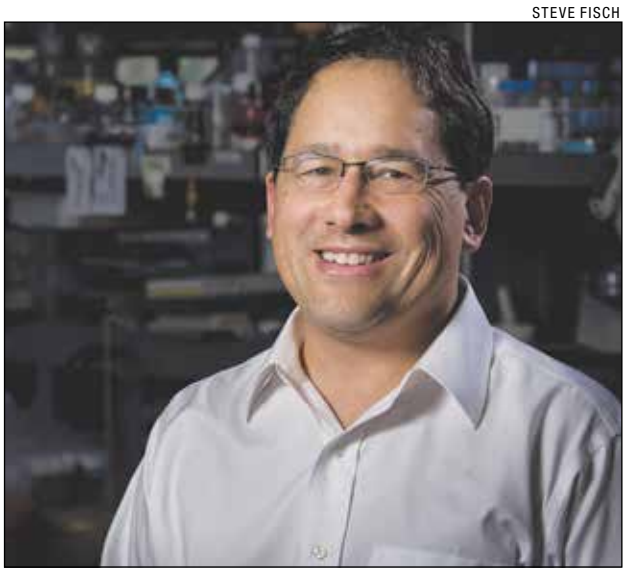
Putting body parts in the right place

Morphogens are responsible for the body patterning that ensures, for example, that a fly's wing ends up on its thorax rather than the top of its head. They were the first important class of proteins identified in the early days of developmental biology, in part because their effect on a developing embryo is so dramatic. Subsequent studies showed that they work through the process of diffusion and can have different effects based on their concentration throughout the embryo. Cells that are near other cells making and releasing the morphogen are exposed to a much higher concentration than those farther away; as waves of varying morphogens overlap and interact, they direct the proper placement of legs, wings and the head, for example.

Soon, researchers also identified other types of proteins called master transcriptional regulators that bind to DNA to control the expression of specific genes throughout the cell. But they quickly learned that each of these regulators could spark the formation of vastly different cell types, and it was unclear how each regulator knew to favor the development of one tissue type over another.

Oro and his colleagues were studying the effect of two well-known morphogens involved in skin development — BMP4 and retinoic acid — on the activity of a master transcriptional regulator called p63 that is responsible for tissue types as diverse as skin, thymus and the lining of the esophagus.

STEVE FISCH



Anthony Oro and his colleagues have identified a key regulatory hierarchy in which proteins called morphogens control gene expression by directing the looping of DNA in a cell.

In particular, they were interested in the process by which human embryonic stem cells can be triggered to develop into keratinocytes to form sheets of skin to repair the blistering and open wounds seen in people with epidermolysis bullosa. Previous attempts, although somewhat successful, yielded im- **See ORIGAMI, page 7**

Older fathers associated with increased risks for their newborns

By Hanae Armitage

A decade of data documenting live births in the United States links babies of older fathers with a variety of increased risks at birth, including low birth weight and seizures, according to a new study by researchers at the School of Medicine.

The data even suggest that the age of the father can sway the health of the mother during pregnancy, specifically her risk for developing diabetes.

"We tend to look at maternal factors in evaluating associated birth risks, but this study shows that having a healthy baby is a team sport, and the father's age contributes to the baby's health, too," said Michael Eisenberg, MD, associate professor of urology.

Data from more than 40 million births showed that babies born to fathers of an "advanced paternal age," which roughly equates to older than 35, were at a higher risk for adverse birth outcomes, such as low birth weight, seizures and need for ventilation immediately after birth. Generally speaking, the older a father's age, the greater the risk. For example, men who were 45 or older were 14 percent more likely to have a child born prematurely, and men 50 or older were 28 percent more likely to have a child that required admission to the neonatal intensive care unit.

STEVE FISCH

Michael Eisenberg and his colleagues examined data from more than 40 million U.S. births and found links between older fathers and increased health risks for their infant children.

Still, these numbers aren't reason to drastically change any life plans, as the risks are still relatively low, Eisenberg said. He compared the increased risks to buying lottery tickets. "If you buy two lottery tickets instead of one, your chances of winning double, so it's increased by 100 percent," he said. "But that's a relative increase. Because your chance of winning the lottery started very small, it's still unlikely that you're going to win the lottery. This is a very extreme example, but the same concept can be applied to how you think about these birth risks."

Instead, Eisenberg sees the findings as informational ammunition for people planning a family and hopes that they will serve to educate the public and health officials.

A paper describing the study was published online Nov. 1 in the *British Medical Journal.* Eisenberg is the senior author. Resident physician Yash Khandwala, MD, is the lead author.

Increased risks at 35

Back in 2017, Eisenberg published a study showing that the number of older men fathering children was on the rise. Now, about 10 percent of infants are born to fathers over the age of 40, whereas four decades ago it was only 4 percent.

"We're seeing these shifts across the United States, across race strata, across education levels, geography — everywhere you look, the same patterns are being seen," Eisenberg said. "So I do think it's becoming more relevant for us to understand the health ramifications of advanced paternal age on infant and maternal health."

Eisenberg and his colleagues used data from 40.5 million live births documented through a data-sharing program run by the Centers for Disease Control and Prevention and the National Center for Health Statistics. The researchers organized the information based on the fathers' age — younger than 25; 25 to 34; 35 to 44; 45 to 55; and older than 55 — and controlled for a variety of parameters that might skew the association between the father's age and birth outcomes, such as race, education level, marital status, smoking history, access to care and the mother's age.

The data suggested that once a dad hits age 35, there's a slight increase in birth risks overall — with every year that a man ages, he accumulates on average two new mutations in the DNA of his sperm — but birth risks for infants born to fathers of the subsequent age tier showed sharper increases.

Compared with fathers between the ages of 25 and 34 (the average age of paternity in the United States), infants born to men 45 or older were 14 percent more likely to be admitted to the NICU, 14 percent more likely to be born prematurely, 18 percent more likely to have seizures and 14 percent more likely to have a low birth weight. If a father was 50 or older, the likelihood that their infant would need ventilation upon birth increased by 10 percent, and the odds that they would need assistance from the neonatal intensive care unit increased by 28 percent.

"What was really surprising was that there seemed to be an association between advanced paternal age and the chance that the mother would develop diabetes during pregnancy," said Eisenberg. For men age 45 and older, their partners were 28 percent more likely to develop gestational diabetes, compared with fathers between 25 and 34. Eisenberg points out that possible biological mechanisms at play here are still a bit murky, but he suspects that the mother's placenta has a role.

Beyond correlation

Moving forward, Eisenberg wants to look into other population cohorts to confirm the associations between age and birth risks, as well as begin to decode some of the possible biological mechanisms.

"Scientists have looked at these kinds of trends before, but this is the most comprehensive study to look at the relationship between the father's age and birth outcomes at a population level," said Eisenberg. "Having a better understanding of the father's biological role will be obviously important for the offspring, but also potentially for the mother."

Other Stanford co-authors of the study are professor of obstetrics and gynecology Valerie Baker, MD; professor of pediatrics Gary Shaw, DrPH; professor of pediatrics David Stevenson, MD; and professor of biomedical data, Ying Lu, PhD.

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

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

Lax state gun laws linked to more child, teen gun deaths

By Erin Digitale

Gun deaths among children and teenagers are twice as common in U.S. states with the most lax gun laws compared with states with the strictest gun control legislation, a study from the School of Medicine has found.

In addition, states with laws that restrict children's access to guns have lower rates of firearm-related suicides among youth, even after controlling for other factors, the study said.

The research will be presented in a scientific talk today at the American Academy of Pediatrics 2018 National Conference & Exhibition in Orlando, Florida.

The title of the presentation is "Strict Firearm Legislation Is Associated With Lower Firearm-Related Fatalities Among Children and Teens in the United States."

"A child is 82 times more likely to die in our country of a firearm injury than in any other developed nation," said senior author Stephanie Chao, MD, assistant professor of surgery at Stanford. "We focus a lot on the federal government and the things they can do to protect our children from firearms. But our study shows that what states do at the state level really does have an impact."

Stephanie Chao

The lead authors of the study are former graduate student Sriraman Madhavan and postdoctoral scholar Jordan Taylor, MD.

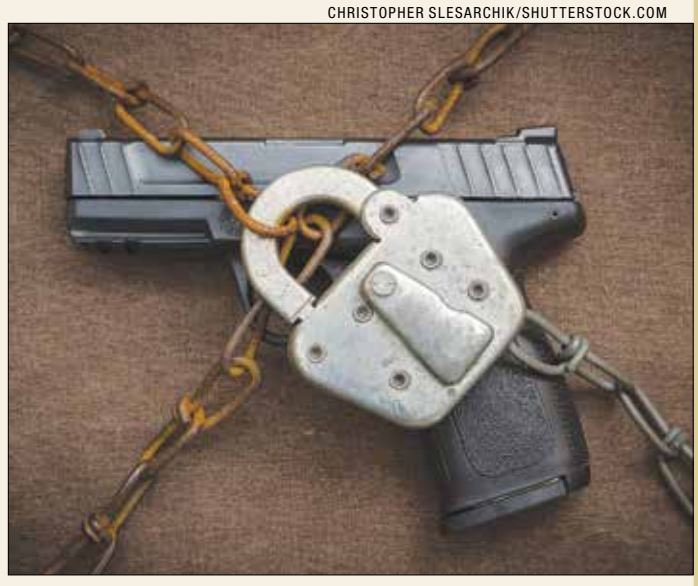
Chao, a pediatric surgeon, is the medical director of trauma care at Lucile Packard Children's Hospital Stanford, where her role includes investigating how to prevent serious childhood injuries. "If you look at what causes injury deaths in U.S. children, sadly, firearms are always in the top five," she said.

Gun death data

Chao's team used 2014 and 2015 data on firearm deaths of individuals 0 to 19 years old from the National Vital Statistics System, which is maintained by the Centers for Disease Control's National Center for Health Statistics. About 2,715 children died of firearm injuries each year. Of those deaths, 62.1 percent were homicides, 31.4 percent were suicides and the remaining deaths were accidental, of undetermined intent or the result of legal interventions.

The researchers examined the firearm laws of all 50 states. They rated the overall stringency of each state's gun laws as of 2014 using a metric called the Brady score, which ranged from -39 in the least strict state, Arizona, to +76 in the strictest state, California. (The score is named for James Brady, who has advocated for gun control since being permanently disabled in the 1981 assassination attempt on Ronald Reagan.) The researchers also evaluated whether each state had child access prevention laws, which were classified in two groups: legislation that requires storing guns safely (locked or unloaded, or both), and laws that impose liability for failing to prevent minors from gaining access to guns.

CHRISTOPHER SLESARCHIK/SHUTTERSTOCK.COM



Analyses of the relationship between gun deaths and gun laws were controlled for many socioeconomic and demographic factors, including unemployment rates, poverty, urbanization, alcohol dependence, tobacco and marijuana use, and high school graduation rates. The analyses also accounted for the strictness of gun laws in each state's neighboring states and the number of registered firearms per 100,000 children in each state.

The researchers grouped the states by Brady score. Before adjusting for socioeconomic and demographic factors, the states in the highest quartile — with the strictest laws — had an annual youth firearm mortality rate of 2.6 per 100,000, while states in the lowest quartile, with the least strict laws, had nearly twice that mortality rate, at 5.0 per 100,000. States' Brady scores were still significantly correlated with pediatric gun deaths after controlling for other factors.

States with both types of child access prevention laws had pediatric firearm suicide rates of 0.63 per year per 100,000 children, while states that had no CAP laws had 2.57 pediatric firearm suicides per year per 100,000 children. The relationship was significant even after controlling for other factors, the study found.

Chao hopes the work will inform state-level legislators. "If you put more regulations on firearms, it does make a difference," she said. "It does end up saving children's lives."

Other Stanford co-authors of the study are Julia Chandler, MD, resident in surgery and graduate student in health policy; and Kristan Staudenmayer, MD, associate professor of surgery.

Stanford's Department of Surgery supported the work. ISM

CD47

continued from page X

The combination of rituximab and Hu5F-G4 has previously been shown to work well in fighting human cancers in animal models, but this is the first published result of a clinical trial of this therapy in humans. The trial builds upon previous studies of CD47 and its role in cancer that were conducted in Weissman's laboratory and funded by the California Institute of Regenerative Medicine and the Ludwig Institute for Cancer Research.

Ranjana Advani

For this clinical trial, participants were administered a combination of Hu5F-G4 and rituximab at 10 clinical centers. All the patients in the study had failed to respond to or relapsed after at least two previous types of therapy. Hu5F-G4 was administered to the patients at slowly increasing dosages to test for adverse reactions to the antibody.

Of the 22 patients enrolled in the trial, 11 showed a clinically significant reduction in their cancers. In eight of those patients, all signs of cancer were eliminated, Advani said. Three other patients in the trial did not respond to the treatment and died due to disease progression.

Although there are many things that can kill cancer cells, the real test of a therapy is whether it can kill the cancer cells without harming normal cells. Advani said she was particularly pleased that the researchers observed only minor side effects in the participants.

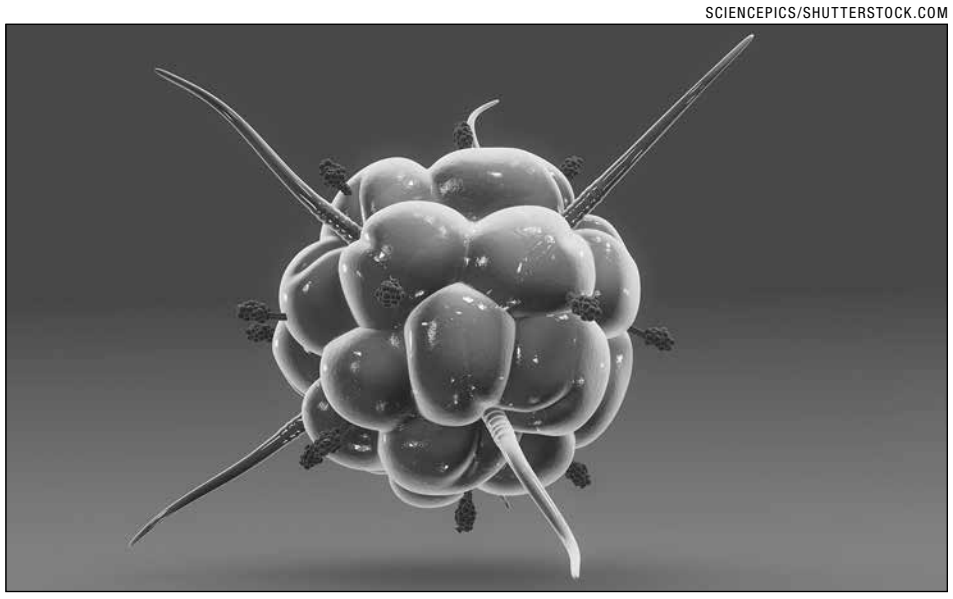
"It's very exciting to have a potentially new class of immunotherapy like this," said Advani, who is the Saul A. Rosenberg, MD, Professor of Lymphoma. "For the first time we have an antibody that activates macrophages against cancer and appears to be safe for use in humans."

Miracle and devastation

Michael Stornetta, a retired Santa Rosa businessman who said he had never previously been sick with anything worse than colds, flus and the usual childhood maladies, was hit with follicular lymphoma over five years ago. He said that after attempting multiple therapies with "varying degrees of success," he was referred to the Hu5F9-G4 trial at Stanford.

In October of 2017, he drove with his wife and son to Stanford to view the first scans that would reveal whether the experimental treatment was working. The scans showed that his cancer was significantly reduced. By strange coincidence, the very day that he learned that the treatment was working, he also learned that his house had burned to the ground in the Sonoma County fires. "It felt like a miracle on one side and devastation on the other," Stornetta says.

SCIENCEPICS/SHUTTERSTOCK.COM



An illustration of a macrophage, a type of immune cell that can engulf and digest cancer cells. Nearly all cancer cells cover themselves with a protein, CD47, that acts as a "don't eat me" signal to macrophages.

Weissman and Ravindra Majeti, MD, PhD, professor of medicine at Stanford, are co-authors of the paper. Weissman is a founder of Forty Seven, and he and Majeti are board members of the company. Other Stanford-affiliated authors are instructor of medicine Mark Chao, MD, PhD, and clinical research coordinator Thu Tran. Chao is a founder of Forty Seven and its vice president of clinical development.

In addition to being members of Stanford's stem cell institute, Weissman and Majeti are also members of the Stanford Cancer Institute and of the Stanford Ludwig Center for Cancer Stem Cell Research and Medicine. Advani also is a member of the Stanford Cancer Institute.

Researchers at the City of Hope, Sarah Cannon Research Institute/Tennessee Oncology, the University of Alabama-Birmingham, Washington University in St. Louis, Levine Cancer Institute, the University of Chicago, the National Cancer Institute, the Dana Farber Cancer Institute and the University of Oxford also contributed to the study.

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

Antlers

continued from page 1

fied two genes that drive the animals' abnormally quick bone generation.

Although the research is still in its early stages, the scientists hope the findings could one day inform more efficient and effective therapies for bone diseases and fractures in humans.

"Right now, we have two focuses: To understand the genetic regulation of deer antler growth, and to see if we can use this information to build therapeutic agents to potentially prevent or treat bone diseases such as osteoporosis, or more quickly repair bone fractures," said Peter Yang, PhD, associate professor of orthopedic surgery.

Antlers are essentially regenerating bone, which is rare in the animal kingdom. During the spring, antlers begin to sprout; by winter, they start to shed.

PAUL SAKUMA

Peter Yang holds a jar containing pieces of deer antler. He and his colleagues have identified genes responsible for the rapid growth and hardening of deer antlers.

"Knowing the genetics behind antler regeneration, fast bone growth and mineralization is fundamental to our ultimate therapeutic goal and is critical to understanding rapid bone regeneration in other species, like humans," Yang said.

The genes Yang and his collaborators identified are uhrf1, which supports rapid bone cell proliferation, and s100a10, which supports rapid mineralization, or the hardening of bone tissue. Together, the genes work in a one-two punch fashion, with uhrf1 spurring bone cell generation and s100a10 working to cement the bone's structural matrix.

What lends even more transformative potential to Yang's research is that both uhrf1 and s100a10 are linked to bone development in humans.

A paper detailing the researchers' findings was published online Oct. 30 in the *Journal of Stem Cell Research & Therapy*. Yang is the senior author. Postdoctoral scholar Dai Fei Elmer Ker, PhD, is the lead author.

Going stag

As an orthopedic researcher, Yang never planned to pursue deer antler genetics. But while on vacation in Alaska in 2009, Yang's tour guide rattled off some fun facts about wild deer, and it piqued his curiosity.

"Deer antlers can grow a whopping 2 centimeters per day when it's summertime and their antlers are growing at full speed," Yang recalled from the guide's spiel. "It made me wonder: Are there special genes that are behind this unusually fast bone growth?"

To investigate, Yang and his lab traveled to a deer farm in California where they collected samples of early antler tissue, which is primarily made up of skeletal stem cells. Antlers grow from the top down; so as they grow upward, a reservoir of stem cells remains at the top of the antlers, continuing to proliferate. In early development, antler tissue is soft, much like the cartilage of your nose, making cell sampling an easy task for Yang and harmless for the buck. Only in the second stage of development does the antler mineralize and become rigid.

Back in the lab, the scientists used a variety of techniques to decipher the genetics behind antler growth, including analyses of RNA, a molecule that helps carry out specific gene instructions, and gene "knock-down" and "overexpression" studies, which hinder gene function or rev it up, respectively. Comparative RNA analyses between stem cells in deer antlers and human stem cells from bone marrow led Yang to a collection of genes that seemed to have a unique expression in antlers. From that pool, he narrowed the search by tampering with gene function, watching to see how different levels of gene expression affected tissue growth in mouse cells.

In deer antler cells, Yang saw that when the uhrf1 gene was decommissioned, the skeletal stem cells could still grow, just not as quickly; only when uhrf1 was fully functional did the scientists see the rapid cell proliferation characteristic of antler growth. Likewise, when s100a10 was overexpressed, calcium deposits increased and the engineered cells more rapidly mineralized.

"Antler regeneration is a unique phenomenon that, to me, is worth studying just out of pure curiosity, but lo and behold, it may have some really interesting applications for human health," Yang said.

Applying antler genetics to humans

The researchers hope that their insights into antler genes might inform new approaches for treating diseases like osteoporosis. In healthy bones, two types of cells — osteoblasts and osteoclasts — work as opposing forces. Osteoblasts produce new bone tissue, while osteoclasts break down old bone. The two cell types work in a yin and yang style to continuously form and degrade bone to maintain balanced bone structure. In osteoporosis, osteoclast function overtakes osteoblasts, and the bone starts to break down.

"We're just at the beginning of this research, but our ultimate goal is to figure out how we can apply the same underlying biology that allows for rapid bone regeneration in deer antlers to help treat human bone conditions, such as osteoporosis," Yang said.

Yang plans to continue researching multiple kinds of deer to confirm that uhrf1 and s100a10 back speedy antler growth across species. In addition, he plans to test how the genes function in human cell lines, while continuing to parse how uhrf1 and s100a10 work on a molecular level, looking into possible functional pathways.

"There's a lot of work to be done, but this could be a unique model of bone regeneration, and our initial work here has started to lay a foundation for future studies," Yang said.

Other Stanford co-authors of the paper are postdoctoral scholars Dan Wang, PhD, and Bin Zhang, PhD; Norma Neff, PhD, former DNA sequencing core director; former undergraduate researcher Rashmi Sharma; William Maloney, MD, the Boswell Chair of Orthopaedics and professor of orthopedic surgery; and Steven Quake, PhD, professor of bioengineering and of applied physics and co-president of the Chan Zuckerberg Biohub.

Peter Yang is a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Stanford Child Health Research Institute and the Stanford Neurosciences Institute.

Scientists from the Tenth People's Hospital of Tongji University, Calico Life Sciences and the State Key Lab for Molecular Biology of Special Economic Animals also contributed to the study. **ISM**

5 QUESTIONS

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

What parents should know about poliolike illness

Recently, cases of a poliolike illness have been back in the news. Acute flaccid myelitis, a rare complication from certain viral infections, causes paralysis in one or more limbs and strikes mostly children. Keith Van Haren, MD, assistant professor of neurology and neurological sciences at the School of Medicine, has studied the condition and written scientific review articles covering clusters of cases dating back to 2012.

Van Haren talked with science writer Erin Digitale about what parents should know about the disease.

1 What do we know about the history and causes of this condition?

VAN HAREN: There are cases of infectious paralysis stretching far back into recorded human history, including, of course, of poliomyelitis. The best interpretation of current and historical evidence suggests these cases are primarily caused by viral infections, and there happen to be several viruses that can do this. Broadly speaking, we could classify poliomyelitis as a form of acute flaccid myelitis; they appear to share similar elements of pathophysiology.

Enteroviruses — including the three human polioviruses, and enterovirus 71 — are the most common culprits. Since at least 2012, there is accumulating evidence that enterovirus 68 can also cause this syndrome. And West Nile Virus can cause this acute flaccid myelitis, although it's from a different family of viruses.

As best we can tell, the modern outbreaks go back to at least 2012, when Carol Glaser and her team at the California Department of Public Health began noticing an uptick in poliolike cases, mostly in kids. It was Carol who first noticed the viral association with enterovirus 68.

The phrase "acute flaccid myelitis" was coined in 2014 by a group of colleagues, including myself, who were trying to come up with an appropriate descriptive term that would disentangle it from the historical association with poliomyelitis and provide a broader framework for characterizing the illness.

The pattern that we're currently seeing is an every-other-year phenomenon. Different years bring different enteroviruses, just as different years bring different strains of flu. In the years enterovirus 68 has been circulating — in 2012, 2014, 2016 and 2018 — we've also seen an increase in cases all clustered in late summer and early fall, which is the time of year that many species of enteroviruses circulate in North America.

2 What happens in children affected with acute flaccid myelitis?

VAN HAREN: The syndrome typically begins with what looks like a traditional systemic illness. This is broadly true of many infectious neurological illnesses: What begins as an otherwise ordinary infection takes a different course in a particular patient, and it's not understood why.

Enterovirus infections typically start and end as benign illnesses, with congestion, fever and a sense of malaise all lasting a few days. In a very small number of individuals, this illness is followed by something more ominous. The earliest symptom among patients who actually develop acute flaccid myelitis is a period of significant pain in the limb, or multiple limbs, often described as aching, tingling or electric shocks. Within the next day or so, the limb becomes weak, and the weakness can progress very quickly, over the course of an hour or two even, to very weak or complete loss of function. Muscles of the face can also be affected.

Keith Van Haren

The weakness may worsen for the next day or for several days before it reaches its low point and stabilizes. In many cases, the weakened limb does gradually recover, though it may not make a full recovery. Most recovery occurs in the first few months, but recovery may continue for years. We have seen apparent improvement continuing, albeit slowly, even as far out as two years after the injury.

Rehabilitation is sometimes possible once the illness is stabilized. Most rehabilitation efforts are taken on a case-by-case basis, and often include strength training and electrical stimulation devices that deliver tiny electrical pulses, applied directly over the muscle. There are also surgical approaches, in which a nerve that is not working is swapped for a nerve that is working to reattain some muscle movement, typically in an arm, but it is not appropriate for everyone and is attempted only in very highly specialized centers. It requires a highly skilled team to identify who might benefit and plan the procedure.

3 How worried should parents be? Is there anything they can or should do to protect their children?

VAN HAREN: With any infectious illness, the youngest and oldest members of population are most vulnerable. This condition is a bit of an exception, as it is primarily affecting younger children.

To date, the best we can offer is a preventive approach: Try to help keep children healthy and clean with regular hand-washing and limited exposure to very sick people.

If a child is sick, parents should encourage him or her to rest and provide normal, appropriate nourishment and hydration. If the child or parent is noticing acute weakness or significant pain in one limb, they should seek medical care promptly.

It's important to remember how rare this disease is. To put it in context, last year there were about 80,000 deaths across the country from the flu; so far this year, there are around 100 or so total cases of acute flaccid myelitis under investigation. Clinicians and scientists are working hard to understand how to make sure it doesn't become more and, ideally, to eliminate it altogether. Analogous eradication efforts have occurred many times, primarily through vaccination.

4 What are experts doing to better understand the illness?

VAN HAREN: The physician community, including child neurologists and infectious disease specialists, is coming together to form working groups to tackle the problem directly. Our general sense now is that this is a serious illness for anyone who is affected, but it remains rare.

Our goal is to understand what's happening well enough to prevent it from becoming more common, and also to develop better modes to treat it. The physician community is seeing a convergence of evidence that suggests enterovirus 68 is responsible for many but not all cases. This community would like more support from public health agencies and funders to try to understand this disease.

5 What do we know now about the illness that we didn't know last time there were a significant number of cases?

VAN HAREN: There has been some really helpful progress in past couple of years in terms of modeling around enterovirus 68, focusing on the biology of the virus. Scientists have studied the genetic alterations that may have made the virus more prone to attack the human nervous system, and have tested the ability of the virus to do this in a mouse model. This is a crucial foundation for developing treatments and vaccinations.

It's somewhat disappointing that we don't yet have a good therapeutic or really specific preventive approach. Those are the areas we ought to be making ardent strides toward. ISM

Apple

continued from page 1

this second app.

"The advantage of the app that uses the optical sensor is that it can check for an irregular pulse multiple times throughout the day in the background, without needing the user to actively engage the application," Perez said.

Goals of the study

Each year in the United States, atrial fibrillation results in 130,000 deaths and 750,000 hospitalizations, according to the Centers for Disease Control and Prevention. The CDC estimates that the condition affects between 2.7 million and 6.1 million people. In addition, another 700,000 people may have undiagnosed atrial fibrillation.

Each participant in the study is required to have an Apple Watch (series 1, 2 or 3) and an iPhone. An app on the phone intermittently checks the heart-rate pulse sensor for measurements of an irregular pulse. If sufficient episodes of an irregular pulse are detected, then the participant receives a notification and is asked to schedule a visit with a doctor involved in the study. Participants are then sent electrocardiography patches, which record the electrical rhythm of their hearts for up to a week.

The goals of the study are threefold: to determine how many among those who receive irregular pulse notifications are found to have atrial fibrillation on ECG patch monitoring; to determine how many among those who received an irregular pulse notification go on to get medical attention; and to determine the accuracy of irregular-pulse detection by the watch by comparing it with the simultaneous ECG patch recordings.

"We now have access to high-quality sensors that can measure and detect changes in our bodies in entirely new and insightful ways without even needing to go to the doctor, but we need to rigorously evaluate them," Turakhia said. "There's never really been a study like this done before."

A subset of the study data was used by Apple as part of its regulatory submission for FDA clearance of the smartwatch app that analyzes pulse-rate data. Apple Heart Study investigators were aware of the submission, but have not seen the submission data.

"We are inspired by the overwhelming response to the Apple Heart Study," said Sumbul Desai, MD, vice president of Apple. "Through the combined power of our participants, Apple Watch and Stanford Medicine, it's one of the largest and most novel atrial fibrillation studies to date."

Researchers from the Lankenau Heart Institute, Jefferson Medical College, the University of Colorado School of Medicine, Cooper Medical School of Rowan University, StopAfib.org, the American Foundation for Women's Health and Duke University also contributed to the paper. ISM

Origami

continued from page 4

pure populations of cells that are difficult to use therapeutically. In search of a more reliable way to produce the cells, they wondered if they could generate keratinocytes by exposing the stem cells to a defined combination of morphogens and transcription factors. To do so, however, they experimented with when, and how much, of each component to add and watched how the cells reacted.

Synergistic feedback loop

The researchers found that, although p63 is required to make skin cells from embryonic stem cells, it is not sufficient. In the absence of BMP4 or retinoic acid, nothing happens, even if p63 is snuggly bound to its landing pad on the DNA. However, when BMP4 or retinoic acid is added, the DNA conformation changes, and p63 begins transcribing skin-specific genes. This dependence of p63 activity on the presence of morphogens was unexpected and telling.

"Basically, p63 binds to the DNA, and then sits back and waits, twiddling its thumbs, until it is connected to specific genes by the morphogen-caused folding," Oro said. "Or sometimes the DNA folds weeks or months in advance, and this foreshadowing sets up a particular differentiation plan, poising the chromatin to assume a specific fate when the transcriptional regulator is added."

Additionally, the researchers discovered that exposing the stem cells to retinoic acid and BMP together also triggered the expression of p63, indicating a complex and synergistic feedback loop that controls skin development.

"Now we have the tools necessary to understand how the DNA folds and unfolds in response to changing conditions," Oro said. "Deciphering this chromatin origami is critical to learning how to make specific cell types for use in tissue replacement therapies. We know now that certain combinations and concentrations of morphogens cause the cells to fold their DNA in a certain way, while another stimulates the DNA to assume an entirely different conformation. Making specific cell types is not a random event, and we can work to harness and accelerate this process to generate all kinds of transplantable tissues."

Other Stanford authors are technicians Jessica Torkelson, Elizaveta Bashkirova and Hanson Hui Zhen; postdoctoral scholars Lingjie Li, PhD, and Xiaomin Bao, PhD; graduate students Adam Rubin and Maxwell Mumbach; undergraduates Eric Liaw, Daniel Alber and Charlotte Rajasingh; informatician Gautam Shankar; professor of dermatology and of genetics Howard Chang, MD, PhD; and professor and chair of dermatology Paul Khavari, MD, PhD. ISM

Stanford Children's Health announces appointment of new CEO

Paul King has been selected as the new president and CEO of Lucile Packard Children's Hospital Stanford and Stanford Children's Health. The organization's board of directors announced King's appointment Nov. 2.

King, who is currently executive director of the University of Michigan Health System's C.S. Mott Children's Hospital and Von Voigtlander Women's Hospital, will succeed Dennis Lund, MD, who has served as interim president and CEO of Stanford Children's Health since March.

"With more than 35 years in health care, including 22 years in executive roles leading pediatric healthcare enterprises, Paul brings a wealth of experiences and leadership expertise to Stanford Children's Health," said Jeff Chambers, chair of the board of Stanford Children's Health.

King has led Mott Children's since 2013, where his management efforts helped the organization achieve the highest patient satisfaction and employee engagement levels across the entire University of Michigan Health System. Prior to that, he served as president and CEO of the Pediatric Management Group, a 550-physician academic pediatric subspecialty group practice affiliated with Children's Hospital Los Angeles.

"As we plan for the continued growth of Stanford Children's Health and expansion of innovation across the entire continuum of care, Paul's distinguished record of accomplishment and dedication to the critically important role of pediatric and obstetric care will undoubtedly help us achieve our vision of precision health at Stanford Medicine," said Lloyd Minor, MD, dean of the School of Medicine.

Paul King

"I am thrilled to be joining Stanford Children's Health at a time of flourishing innovation in pediatric health care," King said. "The possibilities that are within reach for the world-class Stanford Medicine academic medical institutions are truly limitless. I look forward to working with the board and executive leadership, the physicians and staff, as well as with partners at the School of Medicine and Stanford Health Care, to continue to advance pediatric care and research and raise the bar for patient experience and outcomes not just for our patients, but for children and expectant mothers everywhere."

King earned a bachelor's degree in business administration and economics from the University of Nebraska, and a master's degree in health care administration from the University of Iowa. He serves on several boards, including those of the Children's Hospital Association and the American Hospital Association Maternal & Child Health Council.

Lund stepped into the interim CEO role at Stanford Children's Health in March, when Christopher Dawes announced his retirement and medical leave of absence. Dawes had served as president and CEO since 2000.

In a joint statement, Minor and Chambers said that Lund "has demonstrated exceptional leadership during this challenging time while also successfully spearheading the opening of the new state of the art Bonnie Uytengsu and Family Surgery and Interventional Center. We also thank Chris for his extraordinary contributions to Packard, Stanford and children's health nationwide over his remarkable career."

King is expected to begin his new role at Stanford Children's Health in early 2019. More detailed plans for his transition will be announced in the coming weeks. **ISM**

OF NOTE

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

Gregory Bean

Alistair Boettiger

Dylan Dodd

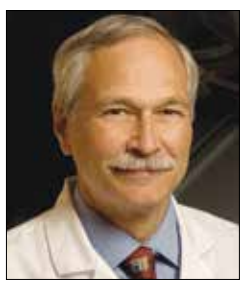
Laramie Duncan

Okyaz Eminaga

Meghan Rice

Shai Friedland

Sanjiv "Sam" Gambhir



Richard Hoppe

Ravi Majeti

GREGORY BEAN, MD, PhD, was appointed assistant professor of pathology, effective Aug. 1. His research focuses on the molecular characterization of benign and malignant breast tumors. His specific interests are identifying and understanding pathologic and genomic features of breast cancer subtypes, precursor lesions and tumor progression.

ALISTAIR BOETTIGER, PhD, assistant professor of developmental biology, was awarded a 2018 Packard Fellowship in Science and Engineering from the David and Lucile Packard Foundation. Fellows are granted $875,000 over five years to pursue their research. Boettiger investigates how the three-dimensional structure and organization of the genome regulates gene expression and cell fate in embryonic development.

DYLAN DODD, MD, PhD, was appointed assistant professor of pathology, effective Aug. 16. His research examines the chemistry underlying host-microbe interactions in the gut, with the goal of improving health and treating disease.

LARAMIE DUNCAN, PhD, was appointed assistant professor of psychiatry and behavioral science, effective Sept. 1. Her research explores how genetics and the environment affect mental health, with the goal of discovering fundamental information about psychiatric disorders and building new approaches to classify, prevent and treat them.

OKYAZ EMINAGA, MD, PhD, postdoctoral scholar in urology, and **MEGHAN RICE**, PhD, postdoctoral scholar in radiology, have received Prostate Cancer Research Program Early Investigator Research Awards from the Department of Defense. The grants, $314,000 each, will support their research for two years. Eminaga plans to develop computer-aided diagnostic and prognostic tools that identify and localize significant prostate cancer lesions. Rice intends to investigate the mechanisms underlying the development of aggressive prostate cancer, identify therapeutic targets in prostate cancer, and develop strategies for the use of new combination therapies.

SHAI FRIEDLAND, MD, was promoted to professor of medicine, effective Aug. 1. His research focuses on analyzing and developing endoscopic techniques and tools, particularly relating to imaging and treating neoplastic lesions in the gastrointestinal tract.

SANJIV "SAM" GAMBHIR, MD, PhD, the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research and professor and chair of radiology, was appointed to serve on the advisory council of the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health. His term started Sept. 16 and will continue until Aug. 31, 2021.

RICHARD HOPPE, MD, Henry S. Kaplan-Harry Lebeson Professor of Cancer Biology and professor of radiation oncology, received the Karl Musshoff Prize for Clinical Research. The award was given in recognition of his achievements and contributions to the understanding and treatment of Hodgkin lymphoma.

RAVI MAJETI, MD, PhD, was promoted to professor of medicine, effective Sept. 1. In addition, he has received a three-year, $600,000 award from the Leukemia & Lymphoma Society. His research aims to identify molecular and genetic differences between human acute myeloid leukemia stem cells and their normal counterparts, and then to develop therapeutic strategies, including using CAR-T cell therapy.

MARK MCGOVERN, PhD, professor of psychiatry and behavioral sciences, received an award from the U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration. The award provides $500,000 each year for five years to fund the creation of a national coordinating center, based at Stanford, for the Mental Health Technology Transfer Center. A one-year, $300,000 school-based mental health services supplement was added to the award to support efforts against violence at schools.

VJ PERIYAKOIL, MD, associate professor of medicine, primary care and population health, received $2 million from the National Institutes of Aging to develop the Stanford Aging, Geriatrics and Ethnogeriatrics Center. The grant also will support underrepresented minority junior researchers at Stanford who are interested in research on aging.

SHARON PITTERI, PhD, was promoted to associate professor (research) of radiology, effective Sept. 1. Her research focuses on the discovery and validation of proteins that can be used as molecular indicators of the risk, diagnosis, progression and recurrence of cancer.

TAIT SHANAFELT, MD, the Jeanie and Stew Ritchie Professor, professor of medicine and director of the WellMD Center, and **TONY WYSS-CORAY**, PhD, professor of neurology and neurological sciences and senior research career scientist at the Veterans Affairs Palo Alto Health Care System, were named two of *Time* magazine's 50 most influential people in health care for 2018. Shanafelt specializes in physician burnout and prevention, and Wyss-Coray's work focuses on treatments for brain aging.

DERRICK WAN, MD, associate professor of plastic and reconstructive surgery, received an allograft tissue research grant from the Plastic Surgery Foundation and MTF Biologics, a nonprofit service organization. The $100,000 grant will fund two years of his project to develop an approach to reconstruct irradiated soft tissue with decellularized human adipose matrix. **ISM**

Mark McGovern

VJ Periyakoil

Sharon Pitteri

Tait Shanafelt

Tony Wyss-Coray

Derrick Wan