INSIDE STANFORD MEDICINE

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For Laura Hosking, open-heart surgery was considered too risky, so an alternative approach was suggested.

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Cancer 'vaccine' eliminates tumors in mice

By Krista Conger

Injecting minute amounts of two immune-stimulating agents directly into solid tumors in mice can eliminate all traces of cancer in the animals, including distant, untreated metastases, according to a study by researchers at the School of Medicine.

The approach works for many different types of cancers, including those that arise spontaneously, the study found.

The researchers believe the local application of very small amounts of the agents could serve as a rapid and relatively inexpensive cancer therapy that is unlikely to cause the adverse side effects often seen with bodywide immune stimulation.

"When we use these two agents together, we see the elimination of tumors all over the body," said Ronald Levy, MD, professor of oncology. "This approach bypasses the need to identify tumor-specific immune targets and doesn't require wholesale activation of the immune system or customization of a patient's immune cells."

One agent is currently already approved for use in humans; the other has been tested for human use in several unrelated clinical trials. A clinical trial was launched in January to test the effect of the treatment in patients with lymphoma.

Levy, who holds the Robert K. and Helen K. Summy Professorship in the School of Medicine, is the senior author of the study, which was published Jan. 31 in *Science Translational Medicine*. Instructor of medicine Idit Sagiv-Barfi, PhD, is the lead author.

STEVE FISCH

Ronald Levy (left) and Idit Sagiv-Barfi led the work on a possible cancer treatment that involves injecting two immune-stimulating agents directly into solid tumors.

'Amazing, bodywide effects'

Levy is a pioneer in the field of cancer immunotherapy, in which researchers try to harness the immune system to combat cancer. Research in his laboratory led to the development of rituximab, one of the first monoclonal antibodies approved for use as an anti-cancer treatment in humans.

Some immunotherapy approaches rely on stimulating the immune system throughout the body. Others target naturally occurring checkpoints that limit the anti-cancer activity of immune cells. Still others, like the CAR T-cell therapy recently approved to treat some types of leukemia and lymphomas, require a patient's immune cells to be removed from the body and genetically engineered to attack the tumor cells. Many of these approaches have been successful, but they each have downsides — from difficult-to-handle side effects to high-cost and lengthy preparation or treatment times.

"All of these immunotherapy advances are changing medical practice," Levy said. "Our approach uses a one-time application of very small amounts of two agents to stimulate the immune cells only within the tumor itself. In the mice, we saw amazing, bodywide effects, including the elimination of tumors all over the animal."

Cancers often exist in a strange kind of limbo with regard to the immune system. Immune cells like T cells recognize the abnormal proteins often present on cancer cells and infiltrate to attack the tumor. However, as the tumor grows, it often devises ways to suppress the activity of the T cells.

Levy's method works to reactivate the cancer-specific T cells by injecting microgram amounts of two agents directly into the tumor site. (A microgram is one-millionth of a gram). One, a short stretch of DNA called a CpG oligonucleotide, works with other nearby immune cells to amplify the expression of an activating receptor called OX40 on the surface of the T cells. The other, an antibody that binds to OX40, activates the T cells to lead the charge against the cancer cells. Because the two agents are injected directly into the tumor, only T cells that have infiltrated it are activated. In effect, these T cells are "prescreened" by the body to recognize only cancer-specific proteins.

Cancer-destroying rangers

Some of these tumor-specific, activated T cells then leave the original tumor to find and destroy other identical tumors throughout the body.

The approach worked startlingly well in laboratory mice with transplanted mouse lymphoma tumors in two sites on their bodies. Injecting one tumor site with the two agents caused the regression not just of the treated tumor, but also of the second, untreated tumor. In this way, 87 of 90 mice were cured of the cancer. Although the cancer recurred in three of the mice, the tumors again regressed after a second treatment. The researchers saw similar results in mice bearing breast, colon and melanoma tumors.

Mice genetically engineered to spontaneously develop breast cancers in all 10 of their mam- See CANCER, page 6

Talking to doctors about your bucket list could help with treatment planning

By Tracie White

For physicians, asking patients about their bucket lists, or whether they have one, can encourage discussion about making their medical care fit their life plans, according to a study by researchers at the School of Medicine.

A bucket list is a list of things See BUCKET, page 7

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Surgeons perform 'bloodless' open-heart operation

By Erin Digitale

Physicians at Lucile Packard Children's Hospital Stanford have performed open-heart surgery without a blood transfusion on the smallest infant ever to undergo such a procedure in North America.

The surgery was done on a 10-day-old baby girl born in Hemet, California, with a serious congenital heart defect. Meticulous planning and execution of the surgery, an arterial switch procedure, allowed the medical team to surmount daunting technical challenges of treating a 7-pound open-heart patient without giving her a blood transfusion. It is the first "bloodless" open-heart surgery performed on an infant in the Western United States.

COURTESY OF THE GARCIA FAMILY

Lola Garcia with her brother C.J. The baby girl had open-heart surgery without a blood transfusion when she was 10 days old.

"If you can do surgery safely and effectively without transfusion, there are several medical benefits," said Frank Hanley, MD, chief of pediatric cardiac surgery at the hospital's Betty Irene Moore Children's Heart Center and one of two surgeons who performed the procedure. He said patients who do not receive blood products have fewer post-surgical complications, provided they do not lose too much blood.

"You have to be able to do the surgery safely and not have the patient's red blood cell count drop too low," added Hanley, who is the Lawrence Crowley, MD, Professor in Child Health at the Stanford School of Medicine.

A severe heart defect

From the moment of her birth on Oct. 21, little Lola Garcia struggled to breathe. She and her parents, Felisa and Jared Garcia, were rushed to a children's hospital near the family's home.

Lola was diagnosed with transposition of the great arteries, a rare condition in which the heart's major arteries are not connected correctly. Normally, the blood follows a single, figure-eight-shaped circuit through the heart and lungs, then back to the heart and out to the body to supply oxygen to organs. In Lola's heart, the blood See BLOODLESS, page 6

Dynamic DNA dance identified with CRISPR-based labeling

By Krista Conger

DNA flails about during transcription like a strand of spaghetti being sucked through pursed lips, School of Medicine researchers have found. Like the resulting out-of-control flying globs of sauce, the surprising discovery flies in the face of conventional wisdom, which posits that static loops of DNA are required to bring together distant regions that enhance and promote gene expression.

A new DNA labeling technique, which can precisely tag any individual stretch of DNA with fluorescent molecules to track their three-dimensional locations and movements, revealed this genetic dance. The technique, which the researchers have termed CARGO, for chimeric array of gRNA oligo, is a variation of the CRISPR/Cas9 gene-editing tool, and it promises to revolutionize the study of genome dynamics.

MISHA GRAVENOR

Joanna Wysocka and her lab team found that DNA twitches during transcription to bring distant regions in contact and enhance gene expression.

'Counters the prevailing beliefs'

"We've found that, as the polymerase plows across the DNA, it provides a source of molecular agitation that increases mobility within a local chromosome domain and can repeatedly bring distant regions of the genome together," said Joanna Wysocka, PhD, professor of developmental biology and of chemical and systems biology. "This was entirely unexpected and surprising, and directly counters the prevailing beliefs about transcription. It's just one example of what we and others can now learn by using CARGO to label specific DNA regions."

> "This was entirely unexpected and surprising."

A paper describing the research was published Jan. 25 in *Science*. Wysocka is the senior author, and graduate student Bo Gu is the lead author.

CRISPR is most commonly used to seek out and replace specific DNA sequences in the genome with other DNA sequences. To do so, an enzyme called Cas9 uses a short RNA sequence to guide the DNA sequences to the correct spot in the genome.

A variation of the technique that was developed by other researchers instead uses guide RNAs and the CRISPR system with a catalytically inactive form of Cas9 to recognize and label specific stretches of DNA with fluorescent molecules. But that works best on highly repetitive regions where a single guide RNA can marshal the critical mass of fluorescent tags necessary to generate enough light to be seen through a microscope.

'CARGO solves the delivery problem'

Wysocka, Gu and another co-author of the study, Tomasz Swigut, PhD, devised a way to introduce an array of many different guide RNAs into a cell to precisely recognize nonrepetitive, unique stretches of DNA and label them with multiple fluorescent tags so they can be easily visualized under a microscope.

"All the most interesting stuff in the genome is present as single copies," Wysocka said. "People have been trying unsuccessfully to label single regions, or loci, for some time. But CARGO solves the delivery problem. Now we can label any region, or locus, that we want by using many different guide RNAs to blanket the DNA so we can see it clearly." She and Gu emphasize that the CARGO technique will be useful to researchers pursuing many different questions about the genome or gene expression.

Already it's opened their eyes about the process of transcription, which is often stimulated when distant enhancer regions are brought into close proximity with other DNA regions called promoters.

"We found that any locus we looked at moved about four times faster in its active state, when nearby genes are being transcribed into RNA," Wysocka said. "We propose that this enhanced movement, or diffusion, is likely to bring distant regions of the DNA together and further promote transcription."

Other Stanford authors of the study are graduate students Andrew Spencley and Mingyu Chung; former research technician Matthew Bauer, and professor of chemical and systems biology Tobias Meyer, PhD.

Gu, Swigut and Wysocka have filed a U.S. provisional patent application relating to the CARGO methodology.

The research was supported by the National Institutes of Health (grant GM112720), the Howard Hughes Medical Institute and a Stanford graduate fellowship.

Stanford's departments of Developmental Biology and of Chemical and Systems Biology also supported the work. ISM

Sanitation improves health but not stunted growth in Bangladesh trial

By Rachel Leslie

Despite mounting research over the last decade linking poor sanitation to stunted growth in children, a new study found that children born into housing compounds with improvements in drinking water quality, sanitation and handwashing infrastructure were not measurably taller after two years compared with those born into compounds with more contamination — although children who received the interventions were significantly healthier overall.

The WASH Benefits Bangladesh trial, led by Stanford epidemiologist Stephen Luby, MD, professor of medicine, is one of the first to examine what are known as water, sanitation and hygiene, or WASH, interventions as a way of improving children's growth in low-income communities. How well a child grows in the first year can indicate overall well-being and is linked to both survival and brain development. These WASH interventions have been proposed as a way of improving child growth and are being implemented in many communities around the world, but haven't been rigorously tested.

> "Modest efforts to marginally improve environments are not going to be sufficient."

"Part of what we learned is that this problem of stunting is not going to be easily fixed by a little bit of attention to water, sanitation and hygiene," Luby said. "Modest efforts to marginally improve environments are not going to be sufficient. If we want children in the lowest-income, most resource-constrained environments to thrive, we're going to need to make their environments radically cleaner."

Children in the Bangladesh trial who received nutritional supplements in addition to WASH interventions did grow taller and were less likely to die during the study, but WASH interventions alone did not improve growth.

GMB AKASH

Study data collectors measure a child's growth in Dhaka, Bangladesh, to assess the impact of water, sanitation and hygiene interventions.

Better nutrition needed

The study, published Jan. 29 in *The Lancet Global Health*, examined the health and growth of children from over 5,000 pregnant women in rural Bangladesh after two years. The mothers were grouped according to geographic clusters and randomly assigned to one of six interventions or a control group. The six interventions included: integration of chlorinated drinking water; upgraded sanitation facilities; promotion of handwashing; a combination of chlorinated drinking water, upgraded sanitation and WASH promotion efforts; nutritional supplements; or WASH and nutritional supplements.

After two years, nearly all the interventions reduced diarrhea. Although expected, the result is important because it suggests that families did adhere to the interventions. It also creates hope that WASH interventions could beat back one of the greatest killers of children globally — the World Health Organization estimates 361,000 children under age 5 die as a result of diarrhea each year.

Of all the interventions, providing nutritional supplements in addition to combined water, sanitation and handwashing interventions had the greatest effect on curbing mortality, in addition to improving growth. Children receiving this intervention were 38 percent less likely to die compared to children in the control group.

The way forward

Past research **See LUBY, page 3**

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Paul Costello
Chief communications officer
Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu. Please also contact him to receive an e-mail version of *Inside Stanford Medicine*.

STANFORD MEDICINE

5 QUESTIONS

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

Eugene Roh on serving as Team USA physician

As a boy growing up in South Korea, Eugene Roh traveled to Seoul in 1988 to attend the Summer Olympics. Now a clinical assistant professor of orthopaedic surgery at the School of Medicine, Roh, MD, is returning to his native country as a physician for Team USA at the 2018 Winter Games. He is an expert in sports medicine and treats patients in the Stanford Orthopaedic and Sports Medicine Clinic in Redwood City, as well as Stanford athletes at the Sports Medicine Center at the Arrillaga Center for Sports and Recreation. He specializes in nonoperative diagnosis and treatment of musculoskeletal injuries using ultrasound and regenerative medicine. Recently, writer Grace Hammerstrom got a chance to ask him some questions about his interest in the Olympics and working with athletes.

1 Where does your fascination with the Olympics come from?

ROH: Everything started when I went to the Olympic Games in Seoul with my middle school class in 1988. It was such a pivotal memory in my life. Since finishing my fellowship training in sports medicine and starting my career, I have always been interested in working at the Olympics. And since South Korea, the country where I was born and raised, is hosting again, the timing was right.

2 Why did you want to be a physician for the Olympics?

ROH: Being part of Team USA is a once-in-a-lifetime experience, a dream come true. It's a chance to work with the best medical team in sports medicine, as well as the best athletes in the world. It is also an opportunity to give something back to the country that has provided me so many opportunities. I'm looking forward to sharing the experience with my wife and son, and introducing my son to two cultures, American and Korean, at the same time.

3 How did you become a physician for Team USA?

ROH: I started looking for an opportunity once it was announced that Korea would host the 2018 Winter Olympics. I was introduced to Bill Moreau, the United States Olympic Committee medical director, when I went to Korea to attend a sports medicine conference. Bill invited me to the U.S. Olympic Training Center in Colorado Springs, where I volunteered to work with the athletes. Since I am trained in internal medicine, physical medicine and rehabilitation, and sports medicine, I was able to see patients with a spectrum of sports-related injuries and internal medicine conditions. The Olympic Training Center also uses sports ultrasound, which I routinely use at Stanford.

COURTESY OF EUGENE ROH

Stanford orthopedic surgeon Eugene Roh is serving as a Team USA physician during the Winter Olympics in South Korea.

Ultimately, I was offered a position as a physician for Team USA. Interestingly, the Korean Olympic Organizing Committee had simultaneously invited me to be a venue medical officer for ice hockey. I had to decide between being part of the medical team for Korea, my home country, or the United States, my new home and the country where I live and have a family. I chose to be a physician for Team USA, which is bringing the largest group of athletes to the games. But I will be working as a liaison between both medical teams.

4 What will you be doing at the Olympics?

ROH: As a Team USA physician, I will be in Korea for a month, arriving a week before the Olympics start and staying until the games end. I will be helping to set up the USOC medical clinic on the first floor of the USA athletes' village, and then seeing athletes in clinic. If there are events that need medical coverage, I will be onsite at those games as well. Essentially, I will be on call the entire time. I will also be working at the ice clusters venue where ice skating and ice hockey take place.

5 What do you enjoy about working with athletes?

ROH: They really inspire me. At Stanford, athletes have to be really dedicated to do sports and academics and balance their lives. Their discipline and passion about what they like to do is inspiring. It's not easy work. In those moments where we all feel settled in life, and get a little lazy, we look to the athletes who inspire us to catapult ourselves to the next level. Treating these athletes and then seeing them being able to go back and play at a high level gives me a lot of fulfillment. I don't care if they score or not. I am gratified by the basics of their walking or moving their arms, especially if they were in severe distress prior to their treatment. If they're able to move well again, it's rewarding. If they do really well, it's a bonus. ISM

Luby

continued from page 2

has shown that WASH strategies are effective at reducing diarrhea and improving child health, Luby said, but evidence of the impact of these strategies on child growth and development has been sparse.

In response to this lack of data, Luby began laying the groundwork for the current study more than a decade ago. One of his concerns was ensuring the group developed a rigorous and transparent trial design that included close community partnerships and innovative ways of encouraging village residents to adopt new behaviors. Unless most people in the community adopted the interventions, he knew the results would not be conclusive.

With the large number of children in the study, good adoption of the interventions and careful design, the study had the statistical power to detect small effects. Thus, Luby noted the absence of growth improvement with WASH interventions was genuine.

"We developed an intervention that the community really liked and were able to achieve really high uptake," said Luby. "What this tells us is that these interventions, even with high uptake, likely didn't clean the environment enough to impact child growth. This is a disappointment, but it also helps to provide direction as a way forward."

While a great amount of knowledge has been gained from the primary outcomes data, Luby and his team are continuing to analyze the broader range of health benefits that could have resulted from these successfully integrated WASH strategies, such as the impact on bacterial, parasitic and viral infections, anemia and nutritional biomarkers, and child cognitive development.

Luby is a senior fellow at the Stanford Woods Institute for the Environment and at the Freeman Spogli Institute for International Studies. He also serves as the director of research for the Stanford Center for Innovation in Global Health.

Co-authors of the publication include scientists from the International Centre for Diarrhoeal Disease Research in Bangladesh, UC-Berkeley, the Johns Hopkins Bloomberg School of Public Health, UC-Davis, Emory University and the University of Buffalo.

The research was supported by the Bill & Melinda Gates Foundation.

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

Stanford Global Health awards funding to 9 projects

The Stanford Center for Innovation in Global Health has awarded $350,000 in seed funding to nine multidisciplinary teams of investigators whose work offers a novel and interdisciplinary approach to improve the health of underserved populations worldwide.

"The main goals of our seed grant program are to encourage and support the growth of Stanford's vibrant global health community and help early stage projects get off the ground," said Michele Barry, MD, director of the Stanford Center for Innovation in Global Health.

The program has jump-started nearly 40 projects, many of which have gone on to receive follow-on funding support, since it began in 2012.

With the support of new funding partners, including the Stanford Child Health Research Institute and the Sean N. Parker Center for Allergy and Asthma Research, this year's grants include projects that address global health challenges related to maternal and child health; allergies, asthma or other respiratory diseases; and health implications of climate change.

Following is a list of the projects that received seed funding and their lead investigators:

• "Noninvasive diagnosis of tuberculosis through detection of cell-free DNA in plasma and urine" — Niaz Banaei, MD, associate professor of pathology and of medicine.

• "Improving the humanitarian response to civilians injured on the modern battlefront" — Sherry Wren, MD, FACS, professor of surgery, and Paul Wise, MD, MPH, professor of pediatrics.

• "Mobile-izing community health workers: A randomized controlled trial in Malawi" — Pascaline Dupas, PhD, associate professor of economics.

• "Impact of a novel barrier repair therapy on the skin and gut microbiome and the prevention of atopic diseases in children in Bangladesh" — Gary Darmstadt, MD, MS, professor of pediatrics, and Natalie Fischer, PhD, postdoctoral scholar in infectious diseases.

• "Gut microbiota acquisition and maturation over the first two years of life in a cohort of rural Bangladeshi children assessed for environmental enteric dysfunction" — David Relman, MD, professor of medicine and of microbiology and immunology, and Elizabeth Costello, PhD, research scientist in medicine.

• "Machine learning for eye care in Nepal: Expanding access and improving care" — Robert Chang, MD, assistant professor of ophthalmology.

• "Relationship of typhoidal Salmonella in water with human typhoid fever and climate" — Jason Andrews, MD, assistant professor of medicine, and Alexander Yu, MD, MPH, clinical fellow in infectious diseases.

• "Mental health issues and violence among adolescents in the Nairobi slums: Can empowerment programs prevent or mitigate both?" — Clea Sarnquist, DrPH, MPH, senior research scholar and lecturer in pediatrics, and Michael Baiocchi, MD, assistant professor of medicine.

• "Linguistic and cultural adaptation of the Building Empowerment and Resilience Program for adolescent girls in Gujarat, India" — Jennifer Keller, PhD, clinical associate professor of psychiatry and behavioral sciences. ISM

Memorial service for Juergen Willmann scheduled for March 22

A memorial service for Juergen Willmann, MD, professor of radiology, is scheduled for 2:30 p.m. March 22 at Stanford Memorial Church. Willman died Jan. 8 in a car accident on Page Mill Road near Palo Alto.

The event is open to members of the Stanford community.

If planning to attend, RSVP to Elizabeth Gill at eagill@stanford.edu by March 15. Please arrive no later than 2:10 p.m. at the church entrance. The event will be followed by a reception at the Faculty Club. ISM

Joseph Woo takes on the challenge of repairing aortic valves

By Ruthann Richter

Nathan Healey was in the prime of his life, a tennis pro who had been a contender at the Australian Open, when his heart erupted. A seemingly healthy 32-year-old, he was puttering around his house in Reading, Pennsylvania, when he felt a tightness in his chest.

"All of a sudden, I felt dizzy, and my heart rate was rising. I guess that is when something blew inside," Healey, 37, recalled recently from his home near Sydney, Australia.

An ambulance ferried him to the local emergency room, where doctors found that a hole had ruptured in the center of his heart, releasing a stream of blood into his system. Healey was transferred to the University of Pennsylvania medical center, where the cardiac surgeon on call, Joseph Woo, MD, greeted him before midnight with some grim news.

"I remember hearing Dr. Woo say, 'Chances aren't good, but I will see what I can do,'" Healey recalled.

Woo, now professor and chair of cardiothoracic surgery at Stanford, discovered that Healey had been born with some previously undetected heart defects, including a weak spot that had progressively enlarged and finally burst open. He had other abnormalities in his aorta, including an aortic valve whose three flaps were of different sizes, making it hard for the valve to close properly. The aortic valve opens and shuts to control the flow of blood from the left ventricle of the heart into the aorta.

In the operating room, Woo faced an urgent decision: Should he try to repair the defective valve, using Healey's own tissue, or should he just replace it with a mechanical or animal valve, as was the more standard procedure?

Woo knew that Healey's athletic career would be over if he replaced the faulty valve, as the replacement options either would not be durable enough or would require him to take lifelong medications that would limit his physical activities.

COURTESY OF JOSEPH WOO

An aortic valve as seen during a surgery to repair it, as well as to replace a diseased section of the aorta with a Dacron tube.

He decided to take the extraordinary step of repairing the valve, doing some creative trimming and sculpting. He cut out one of the three oddly shaped flaps and used that tissue to fashion two flaps of equal size. He also rebuilt some of the surrounding tissues as part of the seven-hour procedure that saved Healey's life and livelihood.

"It was an epiphany," Woo said. "We're always thinking, 'How do you use what's there and take advantage of it? That's the fundamental concept to natural valve repair — to use what's there in whatever creative manner you can to design something that works."

That philosophy has put Woo in the forefront of the movement toward natural valve repair, which evolves as surgeons devise new techniques and gain experience.

Valve-treatment history

Modern-day valve treatment goes back to the 1950s, when the introduction of mechanical valves enabled doctors to replace the diseased tissues with a substitute made of mechanical parts, similar to the valves found in car engines, Woo said. Mechanical valves are effective and last a lifetime, but they have a major drawback in that blood tends to stick to them and form clots. As a result, patients have to take blood-thinning medications, which require regular monitoring for side effects, such as excessive bleeding and stroke.

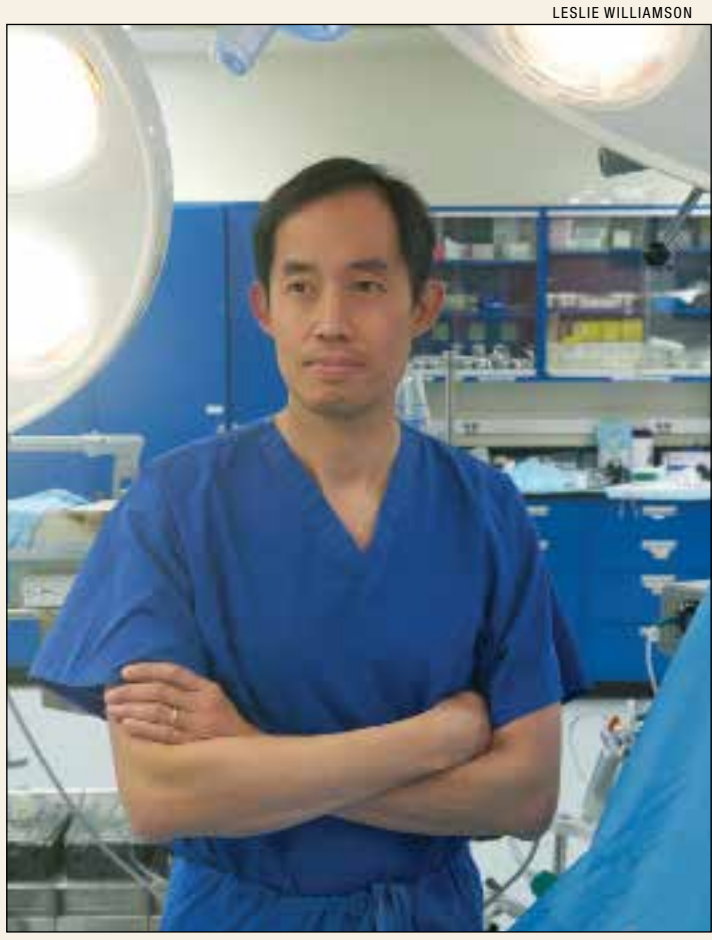
In the 1970s, another alternative came to the fore: prosthetic valves taken from the cadavers of pigs or cows. These can work well but aren't as durable, particularly when used in younger patients, who have greater heart demands. Animal valves can wear out in 10 to 15 years, so patients have to undergo a second replacement and endure the risks of another surgery.

Because none of these replacement options are ideal, surgeons have turned to creatively restructuring damaged valves using the patient's own tissue. Multiple studies have shown that patients who undergo mitral valve repair do better overall: They are more likely to survive, spend less time in the hospital, and suffer fewer complications, such as infection and stroke, compared with those who receive substitute valves, whether animal or mechanical. The mitral valve controls the flow of blood from the left atrium into the left ventricle.

Fixing the aortic valve

While mitral valve repair has gained greater acceptance, aortic valve repair is far less common, as the valve is very different in both form and function. For instance, while the mitral valve has two flaps, the aortic valve has three, so a surgeon has to effectively line up three sides for the valve to open and close properly, Woo said. There is also less tissue to work with in an aortic valve repair, and different techniques and finer sutures are needed, he said.

LESLIE WILLIAMSON



Joseph Woo repairs faulty aortic valves — a difficult, painstaking job that most other heart surgeons decline to do.

In the 1990s, two surgeons, Tirone David, MD, and Sir Magdi Yacoub, MD, pioneered a technique to preserve the aortic valve in patients with an aortic aneurysm, a bulge in the vessel that can cause it to rupture.

In the procedure, known as valve-sparing root replacement, surgeons cut out the diseased part of the aorta and replace it with a tube of Dacron polyester, which is stitched to the heart. Instead of cutting out the aortic valve, as was done in the past, surgeons preserve the patient's tissue and reimplant it inside the new tube, sometimes refashioning the valve to fit the space.

In the operating room

One morning last fall, Woo was called in to perform a variation of this procedure at Stanford Hospital for a man in his 50s who had endocarditis, a heart infection, which had damaged part of his aorta, in-

Potential treatment identified for drug-resistant skin cancer

By Krista Conger

Over half of newly diagnosed advanced or metastatic basal cell carcinomas are resistant to currently approved drug treatments. Yet many of these skin cancers harbor no known resistance-associated genetic mutations, leaving researchers and clinicians wondering how they manage to evade treatment.

Now, researchers at the School of Medicine have identified a link between changes in the cancer cells' internal scaffolding and one of the last steps of the cellular signaling pathway that drives their growth. This previously unknown connection allows the cells to neatly sidestep the effects of currently approved drugs without requiring them to acquire specific genetic mutations.

The researchers found that blocking this connection using an inhibitor previously used to treat inflammation significantly slowed the growth of drug-resistant basal cell carcinomas in mice. Moreover, human primary tumors grown in the lab also responded to the blockade, highlighting the therapeutic potential of this approach.

The findings suggest new ways to tackle the common skin cancer, which affects up to 30 percent of people in the United States at some point in their lives. It also may help researchers better personalize their treatments by identifying patients most likely to respond to certain drugs.

"Many of these tumors are resistant at the time of their diagnosis," said professor of dermatology Anthony Oro, MD, PhD. "Our findings support the idea that tumors have a 'resistance toolbox' of mechanisms from which they can choose, based on their microenviroment, that doesn't depend on genetic mutations often associated with the disease."

Most common cancer in U.S.

A paper describing the research was published online Feb. 5 in *Nature Medicine*. Oro is the senior author, and postdoctoral scholar Ramon Whitson, PhD, is the lead author.

Approximately 2 million new cases of basal cell carcinoma are diagnosed each year in the United States, making it the most common cancer in the country. Most are successfully treated with surgery, and the cancers metastasize only rarely. When they do, however, they can be deadly.

The findings show that the cancer cells sidestep drug treatment by importing a protein into the nucleus that increases the activity of a well-known molecular cascade known as the Hedgehog pathway. This pathway is critical to human development and plays a role in many types of cancer, including pancreatic, colon, lung and breast cancers, as well as to a type of brain cancer called medulloblastoma.

Basal cell carcinomas are uniquely dependent on the inappropriate activation of the Hedgehog pathway. This pathway functions like a Rube Goldberg machine to pass a signal sequentially from outside the cell, across the cell's membrane and into the nucleus to trigger the expression of genes important in cellular growth and development. Each step in the pathway is carried out by the activation or inhibition of specific proteins in the cell.

The cascade begins when the Hedgehog signaling protein, which is secreted by neighboring cells, binds to a receptor called Patched on the surface of cells. Patched then activates another protein on the surface of the cell called Smoothened, which translates the signal across the cell's membrane and into the interior. The final step involves the activation of a protein called GLI1 that binds to and initiates the transcription of specific genes in the nucleus. Most basal cell carcinomas have mutations in Patched or Smoothened, causing runaway activation of GLI1.

Mystery of drug resistance

In 2011, the Food and Drug Administration approved the use of a Smoothened inhibitor called vismodegib, sold under the brand name Erivedge, as a treatment for basal cell carcinoma. About half of patients with advanced basal cell carcinomas will respond to vismodegib, but about 20 percent of these responders

cluding the valve. The patient was put on a heart-lung bypass machine, which took over the function of his heart and lungs while the surgical team did their work. Before Woo began, he viewed the heart on an echocardiogram, displayed on a nearby screen. It showed the valve leaflets flopping back and forth, indicating significant destruction.

He and his team began by cutting out the defective root, then meticulously removing 20 fragments of diseased tissue from around the faulty valve. They replaced the aortic root with an inch-wide Dacron tube, which they anchored in place with multiple blue Gore-Tex sutures. Then came the most challenging part: sewing what remained of the patient's valve back inside the tube.

"Imagine tailoring a suit but from inside the suit," said Woo, as he worked inside the narrow tube, meticulously stitching the valve in place and shaping it so that the leaflets were evenly aligned. It's a procedure many surgeons won't attempt, as there is very little valve tissue left to work with. But for the patient's sake, Woo was determined to make it happen. After more than five hours, he was satisfied with the results: "It's opening up nicely and working beautifully. This guy will keep his own valve over time."

All-repair philosophy

In general, Woo said he likes to approach each patient as a potential candidate for repair, though he realizes it's not always possible. For instance, in patients with aortic stenosis, or a narrowing of the aortic valve opening, the leaflets may be so thickened and damaged by calcium deposits that they can't be manipulated and preserved. But he is nonetheless guided by an all-repair philosophy.

"We believe, in our hands, we can try to approach everyone as potentially reparable," he said. "No one should be viewed as automatically not a candidate. Everyone should have an opportunity."

He said he often gives talks to cardiologists and cardiac surgeons throughout the world, trying to promote the concept and techniques of repair. "It's an ongoing challenge to educate the community that aortic valves can be repaired," Woo said. "Either they have never heard of it or they've never seen it done effectively by a surgeon. Or they don't want to try it out until there is long-term durability data," which is not yet available.

As for Nathan Healey, he fully recovered from his marathon repair procedure after spending 10 days in the hospital. Woo implanted a pacemaker in his heart, as the rupture had disrupted its natural rhythm. Healey was able to return to professional tennis and three years later went on to try his hand in the 2015 U.S. Open — likely one of the few players with a pacemaker to compete at that level.

In the fall of 2016, he moved with his family back to his native Australia, where he now coaches tennis and competes in the occasional tennis tournament.

"I'm just incredibly grateful to be enjoying the life I'm living," he said. "A lot of fortunate pieces fell into place that night. I was lucky to get the surgeon, and I was lucky to get the repair." **ISM**

A longer version of this article appears in the fall 2017 issue of Stanford Medicine *magazine.*

Cancer survivor hits the links again after minimally invasive heart valve replacement

By Grace Hammerstrom

At age 58, Laura Hosking was unusually young to need a new aortic heart valve. But her situation was not typical: As a teenager, she had received treatment for late-stage Hodgkin's lymphoma, including full-body radiation, which put her at risk for problems with her heart and other disorders later in life.

A finance professional and mother of three, she began to feel the long-term effects when she was in her 40s. She tired easily and had difficulty walking and carrying groceries. She could no longer play her usual 18 holes of golf. As her condition worsened over the years, she sought the help of cardiologist Randall Vagelos, MD, who found she was suffering from aortic stenosis, a narrowing of the aortic valve opening that results in restricted blood flow. Her health was further compromised by the discovery in 2013 of lung cancer, which was brought under control with a combination of CyberKnife radiotherapy and localized surgery.

Given these factors, Vagelos, a professor of cardiovascular medicine at the Stanford School of Medicine, knew Hosking might not be able to withstand open-heart surgery, so he offered her the option of a relatively new, minimally invasive heart-valve procedure known as transcatheter aortic valve replacement, or TAVR. The procedure is considered by many in the field as a game-changer. It was approved by the Food and Drug Administration in 2012 for use in patients who, like Hosking, are considered at high risk of complications or death from open-heart surgery.

'A fairly complex history'

"She had a fairly complex history going into the procedure, which made for a heart-team decision favoring the nonopen surgical approach to her valve," Vagelos said. "An open surgical approach to valve replacement in a patient so young is still the gold standard because a mechanical prosthetic valve can last a lifetime. But the global damage to her chest from childhood radiation made a nonopen surgical approach to her aortic valve disease more attractive."

In a traditional aortic valve procedure, surgeons open the chest and use a heart-lung bypass machine to temporarily stop the heart, then remove the damaged valve and replace it with a new one. With TAVR, the new valve is compressed inside a thin catheter, which is inserted into a blood vessel in the leg, then threaded up through the aorta and into the heart. The new valve then is released from the catheter and expanded with a balloon. Once in place, it begins working immediately.

Patients usually recover after two or three days in the hospital, compared with five to seven days for open heart surgery. Hosking, who was younger than a typical TAVR patient, recovered even more quickly. She was walking and talking the day after her procedure, which took place in January 2017, and was back home within two days. She had grown so accustomed to taking shallow breaths for years that she had to retrain herself to breathe normally.

'TAVR gave me back my life'

"TAVR gave me back my life in an immediate and profound way," Hosking said. Today, she has returned to playing golf and clocking 10,000 steps a day. She continues to see her team at Stanford to monitor her new valve and her lungs and said she is immensely grateful to her medical team.

Stanford Medicine doctors have performed more than 1,000 transcatheter aortic valve replacements, and Stanford Hospital is one of a handful of hospitals in Northern California to offer the procedure. Multiple studies have confirmed TAVR's effectiveness in treating patients at intermediate to high surgical risk, and Stanford clinicians are continually evaluating more patients as potential candidates for the procedure. The Stanford team is also studying the use of the approach in patients at all risk levels who have asymptomatic aortic stenosis. **ISM**

COURTESY OF LAURA HOSKING

Laura Hosking underwent a heart procedure known as a transcatheter aortic valve replacement at Stanford Hospital in January 2017.

ANNE DAZEY

Anthony Oro (left) and Ramon Whitson co-authored a study that could help explain why some basal cell carcinomas develop resistance to existing drugs.

will go on to quickly develop resistance to the drug. Oro and Whitson wanted to know why.

Previous work in Oro's lab has identified several mutations that occur in the components of the Hedgehog pathway that cause it to remain active even in the presence of vismodegib. But in about half of resistant tumors, even extensive efforts were unable to identify a responsible genetic mutation.

"We sequenced the heck out of these tumors, and many had no known mutation in genes encoding Hedgehog pathway proteins," said Oro.

When Whitson looked closely at the gene expression patterns of the cells, he noticed that GLI1 — one of the last proteins of the Hedgehog pathway — remained active in the resistant cancers. This active form of GLI1 was found in a complex with another transcription factor called serum response factor. SRF is activated by another protein called megakaryoblastic leukemia 1 that is normally associated with components of the cytoskeleton, or cellular scaffolding, that helps cells maintain their shape and governs their rigidity.

Although MKL1 is normally found primarily in the cytoplasm, Whitson and Oro found elevated levels of the protein in the nucleus of resistant cells when compared with drug-susceptible tumors isolated from human patients. Furthermore, blocking the ability of MKL1 to increase GLI1 activity dramatically slowed the growth of basal cell carcinomas in mice. Additionally, Whitson found that human tumors grown in the lab responded to the MKL1 blockade by reducing GLI1 activity, suggesting this approach may benefit basal cell carcinoma patients.

Because SRF and MKL1 act on one of the last steps of the Hedgehog pathway, they are able to stimulate the cancer cells' growth even in the presence of inhibitors that block steps earlier in the signaling cascade. Intriguingly, changes in a cancer cell's cytoskeleton and shape often enhance its ability to invade surrounding tissues and can lead to metastasis throughout the body.

"People have long associated changes in the extracellular matrix with tumor progression or resistance to drugs," Whitson said. "But this is the first time anyone has identified the molecular causes behind this link. Now we know that we can use the presence of nuclear MKL1 as a biomarker to identify patients who might benefit more from MKL1 or GLI1 inhibitors than from vismodegib."

"This is a common resistance mechanism in a common human tumor," Oro said, "and it doesn't require genetic mutations to turn it on. Understanding this new connection between the cytoskeleton and the Hedgehog pathway will allow us to better personalize treatments to individual patients."

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

Other Stanford authors of the study are graduate students Nicole Urman, Amar Mirza and Catherine Yao; postdoctoral scholars Alexander Brown, PhD, and Jiang Li, PhD; bioinformatician Gautam Shankar; former postdoctoral scholar Scott Atwood, PhD; clinical associate professor of dermatology Tyler Hollmig, MD; clinical professor of dermatology Sumaira Aasi, MD; assistant professor of dermatology Kavita Sarin, MD, PhD; and associate professor of dermatology Jean Tang, MD, PhD.

The research was supported by the National Institutes of Health, a Stanford Epithelial Biology training grant and the Damon Runyon Cancer Research Foundation.

Oro has received funding from Novartis.

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

Cancer

continued from page 1

mary pads also responded to the treatment. Treating the first tumor that arose often prevented the occurrence of future tumors and significantly increased the animals' life span, the researchers found.

Finally, Sagiv-Barfi explored the specificity of the T cells by transplanting two types of tumors into the mice. She transplanted the same lymphoma cancer cells in two locations, and she transplanted a colon cancer cell line in a third location. Treatment of one of the lymphoma sites caused the regression of both lymphoma tumors but did not affect the growth of the colon cancer cells.

"This is a very targeted approach," Levy said. "Only the tumor that shares the protein targets displayed by the treated site is affected. We're attacking specific targets without having to identify exactly what proteins the T cells are recognizing."

> "This is a very targeted approach."

The current clinical trial is expected to recruit about 15 patients with low-grade lymphoma. If successful, Levy believes the treatment could be useful for many tumor types. He envisions a future in which clinicians inject the two agents into solid tumors in humans prior to surgical removal of the cancer as a way to prevent recurrence due to unidentified metastases or lingering cancer cells, or even to head off the development of future tumors that arise due to genetic mutations like BRCA1 and 2.

"I don't think there's a limit to the type of tumor we could potentially treat, as long as it has been infiltrated by the immune system," Levy said.

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

The study's other Stanford co-authors are senior research assistant and lab manager Debra Czerwinski; professor of medicine Shoshana Levy, PhD; postdoctoral scholar Israt Alam, PhD; graduate student Aaron Mayer; and professor of radiology Sanjiv Gambhir, MD, PhD.

Gambhir is the founder and equity holder in CellSight Inc., which develops and translates multimodality strategies to image cell trafficking and transplantation.

The research was supported by the National Institutes of Health, the Leukemia and Lymphoma Society, the Boaz and Varda Dotan Foundation and the Phil N. Allen Foundation.

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

Bloodless

continued from page 1

made two separate circuits — from the heart to the lungs and back, and from the heart to the body and back. The normal figure-eight was separated into two poorly connected loops. Her brain and other organs were not getting enough oxygen.

"They said she would definitely need heart surgery, and most likely a blood transfusion, to correct the problem," said Felisa. "We were happy there was a solution, but when they said 'transfusion,' my heart dropped." The Garcias are Jehovah's Witnesses; they requested that Lola's surgery be done without a blood transfusion because of their religious beliefs.

Although many hospitals now offer bloodless surgery for adults, the challenges of avoiding transfusion are much greater in newborns who need open-heart procedures. Several hospitals around the country turned the family down. But the pediatric cardiothoracic surgery team at Packard Children's offered to attempt baby Lola's arterial switch procedure without transfusing blood.

"Very few people have the technical expertise to do this," said Vamsi Yarlagadda, MD, a clinical associate professor of pediatrics at the School of Medicine and the cardiologist at Packard Children's who cared for Lola.

> "Very few people have the technical expertise to do this."

Technical hurdles

During surgery, Lola needed to be connected to a heart-lung machine, which would pump her blood through a circuit of tubing and membranes for re-oxygenation.

The machine's tubing is primed with saline that mixes with the patient's blood. For an adult, the volume of saline in a standard heart-lung machine does not dilute the blood enough to be dangerous, but a 7-pound newborn has less blood to begin with. Connecting Lola to a standard heart-lung circuit would have dangerously lowered her red blood cell count.

COURTESY OF THE GARCIA FAMILY

Lola, now more than 3 months old, is doing well, according to her parents.

In the past, the problem has been solved by transfusing blood. For Lola, the Packard Children's team took a different approach.

"We used a miniaturized heart-lung circuit so that we could use a much lower priming volume of saline," Hanley said. The team of surgeons, anesthesiologists, cardiologists and other experts also planned every step of Lola's care to minimize blood loss, monitoring her with as few blood draws as safely possible and picking surgical techniques and materials with minimal blood loss in mind.

Hanley and pediatric cardiothoracic surgeon Katsuhide Maeda, MD, clinical associate professor of cardiothoracic surgery at the School of Medicine, operated together to enable them to perform the surgery as precisely as possible. "There were multiple decisions we made before, during and after surgery to minimize the likelihood of bleeding," Hanley said.

Still, the team could not guarantee in advance that Lola would not need a transfusion. California state law gives physicians authority to decide to administer blood to a minor in emergency situations, even if the parents disagree. When they shared their plan with Felisa and Jared Garcia before surgery, the physicians explained the steps they would take to reduce blood loss, and told the parents they had set a safe, lower threshold for Lola's red cell count. "If it reached the threshold, we planned that we would evaluate Lola for negative effects, and if she was showing those, we would give blood," Hanley said.

"Stanford accommodated us really well," said Jared Garcia. During the seven-hour surgery on Oct. 31, the surgeons gave the parents hourly updates on Lola. "We were really nervous, but we were comforted because of those two doctors," Felisa said.

During and after surgery, Lola's red blood cell count stayed in the safe range. As she recovered, the family and doctors soon saw the medical benefits of her bloodless procedure.

"I couldn't believe how fast she was healing," Jared said. "Dr. Yarlagadda had said she would be in the hospital for at least a month, but we went home in less than two weeks. It was great."

Even when the blood type between donor and recipient is matched, transfusions introduce foreign materials into the body, Yarlagadda said. Receiving a transfusion may increase patients' risk of inflammation, and some data suggests that patients who are transfused stay longer in the intensive care unit.

The success of Lola's procedure gives the team confidence that they will be able to continue to reduce their use of blood products, both for medical reasons and to accommodate patients' religious beliefs.

Now 3½ months old, Lola is at home with her parents and 2-year-old big brother, C.J. Her heart is working well, and she's a happy baby who loves to smile at everyone in her family, her parents said.

"Lola is doing fantastic; she looks phenomenal," Hanley said. "Our team is excited to build this program that will help many other children and families in the future." ISM

Tweak to assay could bolster disease detection, according to researchers

By Hanae Armitage

A team of School of Medicine researchers has developed a technique that they hope could more precisely detect diseases or disorders such as cancer or a heart attack.

The technique is an improved method to detect some biomarkers — protein signals in blood or tissues that flag unhealthy or diseased cells. If the biomarker of interest is present, a circle of DNA molecules is created that includes specific proteins, called antibodies, that bind only to the biomarker and a set of DNA sequences that facilitate formation of the circle. If the biomarker isn't there, no circle forms.

A paper describing the technique was published online Jan. 16 in *Proceedings of the National Academy of Sciences*. Ronald Davis, PhD, professor of genetics and of biochemistry, and senior research scientist Henrik Persson, PhD, share senior authorship. Postdoctoral scholar Roxana Jalili, PhD, is the lead author.

Circle formation

The technique, a type of assay, is based on an existing method called a proximity ligation assay, or PLA, which converts the biomarker into a DNA sequence. The modified assay, called circular-PLA, uses additional DNA molecules to generate a circle, a step that enhances the accuracy of the approach.

"In order for the detectable circle to form, the DNA sequences have to be perfect matches with each other," Jalili said. "So, if there's no biomarker, or something incorrectly binds to the biomarker, the DNA sequences won't match, and the circle won't form."

Persson likened the technique to introducing "an extra proofreading step" to PLA.

The extra stringency is particularly important because existing tests yield too many false positives and false negatives, said Davis, who is also director of the Stanford Genome Technology Center.

"There's too much complacency with the existing detection method used in clinics," Davis said. "I think the medical community needs to push back and just not accept it."

Davis sees potential for the technique to help detect biomarkers of diseases with high rates of false positives and negatives, such as human papillomavirus or Lyme disease. He also notes that the ability to accurately detect molecules has many potential applications beyond medicine, such as the identification of mold in a building.

Davis said he hopes clinics and researchers will raise their expectations of biomarker detection methods. "People tolerate the current method because they think, 'Well this is the technology, what are we going to do?'" he said. "But now we actually can do something about it."

Other co-authors are research scientist Joe Horecka, PhD, and James Swartz, PhD, professor of chemical engineering and of bioengineering.

The work was supported by the National Institutes of Health (grant HG000205).

Stanford's departments of Genetics and of Biochemistry also supported the work. ISM

Gift to launch youth addiction, children's concussion initiatives

By Jennifer Yuan

Tad and Dianne Taube of Taube Philanthropies have made two gifts totaling $14.5 million to the School of Medicine and Lucile Packard Children's Hospital Stanford to address addiction and concussions — two of the most significant issues affecting the health and well-being of children and adolescents.

> "When it comes to health, we must think as big as we can."

A gift of $9.5 million will launch the Tad and Dianne Taube Youth Addiction Initiative, a program that aims to comprehensively address the treatment and prevention of addiction during adolescence and conduct research into its causes.

Another gift of $5 million will create the Taube Stanford Concussion Collaborative, leveraging Stanford and Packard Children's medical expertise in collaboration with TeachAids, a Stanford-founded educational technology nonprofit, to advance education, care and research to protect children from concussions.

"As parents, Dianne and I see that young people today are facing a new world of challenges," said Tad Taube, chairman of Taube Philanthropies. "We want to educate families and raise awareness about the risks and signs of addiction and concussion in children and adolescents. It can make an all-important difference in their lives."

Earlier intervention needed

"When it comes to health, we must think as big as we can," said Lloyd Minor, MD, dean of the School of Medicine. "Going after the hardest problems is not only the right thing to do, it is the prudent thing to do. I am immensely grateful to Tad and Dianne Taube for their dedication to Stanford Medicine and their bold commitment to the health and well-being of children and adolescents everywhere."

More than 90 percent of Americans who meet the medical criteria for addiction started smoking, drinking or using other drugs before the age of 18, and Stanford researchers say more needs to be done to advance prevention and intervention efforts during these formative years.

The Tad and Dianne Taube Youth Addiction Initiative will be led by the Division of Child and Adolescent Psychiatry in the Department of Psychiatry and Behavioral Sciences, which has identified advancing the understanding of addiction's causes and addiction prevention and treatment as a priority of the department. Stanford researchers believe the initiative will be the first in the nation to fully address addiction during earliest exposure in adolescence. It is part of a major endeavor at the School of Medicine and Packard Children's to address mental health among young people ages 12 to 25.

Addiction, along with other mental health challenges, is a neglected and stigmatized issue both in adults and young people. Adolescence is a particularly vulnerable time, with hormonal surges and changes in brain development occurring just as young people are facing greater expectations and responsibilities at home and in school, and drug use frequently overlaps with other mental health conditions such as depression and anxiety. Although addiction can take many forms, ranging from drugs to social media, there is evidence to suggest that the underlying neurocircuitry of addiction may be the same.

The Taubes' gift will establish an endowed directorship to organize, launch and lead the youth addiction initiative; an endowed postdoctoral fellowship to train an early career researcher or clinician in child and adolescent mental health with a focus on youth addiction; and endowed faculty scholar awards for three faculty members who will, respectively, focus on clinical care, research and community engagement.

The invisible epidemic

In the United States, the incidence of concussions in children is rising; there are now up to 3.8 million sports- and recreation-related concussions annually. This epidemic, combined with a "tough it out" culture, has led children, parents and coaches to trivialize these head injuries and to allow the athlete to continue playing, which prolongs recovery time and increases the risk of a follow-on concussion.

SAUL BROMBERGER / SANDRA HOOVER PHOTOGRAPHY

Dianne and Tad Taube have donated $14.5 million to launch Stanford initiatives addressing youth addiction and children's concussions.

The Taubes' gift to launch the Taube Stanford Concussion Collaborative will enable Gerald Grant, MD, associate professor of neurosurgery; David Camarillo, PhD, assistant professor of bioengineering; and Piya Sorcar, PhD, a lecturer in the Graduate School of Education, to advance concussion education, care and research to protect children from the cumulative effects of concussions.

"Tad and I share the concerns of fellow parents about the safety of young athletes in our community and beyond," said Dianne Taube. "Our hope through this gift is to ensure the safety of our youth and provide current, useful information to educate parents, coaches and players."

Grant and Camarillo have already made strides in more precisely measuring, diagnosing and treating concussions in young athletes, including Stanford University football and women's lacrosse players. TeachAids, founded by Sorcar, is developing the first comprehensive, research-based educational software that will address misconceptions about concussions, support brain health and safety, and increase the reporting of concussions. By leveraging Stanford technology, TeachAids will deliver an interactive learning experience free of charge, first to Bay Area high schools and eventually up to 10,000 schools nationwide.

Stanford also plans to monitor athletes who use the TeachAids educational platform through a variety of methods, including "smart" mouthguards developed by Camarillo's lab that measure head motion during impact and that eventually may help predict the likelihood of concussion. The data gathered will be analyzed to develop algorithms that will help clinicians predict an individual athlete's risk for concussion and lead to personalized approaches to preventing and treating concussion. **ISM**

Bucket

continued from page 1

you'd like to do before you die, like visiting Paris or running a marathon. It's a chance to think about the future and put lifelong dreams or long-term goals down on a piece of paper.

For doctors, knowing their patients' bucket lists is a great way to provide personalized care and get them to adopt healthy behaviors, said VJ Periyakoil, MD, clinical associate professor of medicine, who said that she routinely asks her patients if they have a bucket list.

"Telling a patient not to eat sugar because it's bad for them doesn't work nearly as well as saying, for example, if you are careful now, you will be able to splurge on a slice of wedding cake in a few months when your son gets married," Periyakoil said.

NORBERT VON DER GROEBEN

VJ Periyakoil encourages physicians to ask patients about their goals and aspirations in order to help personalize their care.

The study was published Feb. 8 in the *Journal of Palliative Medicine.* Periyakoil, an expert in geriatrics and palliative care, is the lead author.

The researchers, who surveyed 3,056 participants across the United States, found that by far the majority of respondents — 91 percent — had made a bucket list. Survey results also showed that respondents who reported that faith and spirituality were important to them were more likely to have made a bucket list. The older the respondents were, the more likely they were to have a bucket list, and, not surprisingly, those younger than 26 tended to include more "crazy things" on their lists, such as skydiving.

Bucket list categories

In the study, six general themes tended to describe the items on respondents' bucket lists: 79 percent included travel; 78 percent included accomplishing a personal goal, such as running a marathon; 51 percent included achieving a life milestone, such as a 50th wedding anniversary; 16.7 percent included spending quality time with friends and family; 24 percent included achieving financial stability; and 15 percent included a daring activity.

"When you just Google the term 'bucket list,' it's huge how much interest there is in this," Periyakoil said. "It provides a very nice framework for thinking about your life goals, health and your mortality."

Past research has found that when doctors talk to patients — especially those with chronic or terminal illnesses — about the patients' goals for future care, it can be a vital part of the advance-care planning process. But it's often awkward to have these conversations, particularly when they are about the end of life, the study said.

"If a patient wants to attend a beloved grandchild's wedding or travel to a favored destination, treatments that could potentially prevent her from doing so should not be instituted without ensuring her understanding of the life impact of such treatments," the study said.

Discussing a patient's bucket list is just a good way to start these conversations, Periyakoil said. Most people are far more open to talking about their life's goals in this context before filling out an advance directive, a written statement of a person's wishes regarding medical treatment at the end of life, Periyakoil said.

'Find out what actually motivates them'

"It's important for physicians to talk to patients and find out what actually motivates them," she said. She encourages both doctors and patients to bring up the topic of a bucket list. By discussing how a treatment or surgery might affect the patient's life, and then discussing what the patient's goals are, the best possible care plan can be laid out, she said.

"I had a patient with gall bladder cancer," Periyakoil said. "He was really stressed because he wanted to take his family to Hawaii but had treatment scheduled. He didn't know he could postpone his treatment by two weeks. When doctors make recommendations, patients often take it as gospel."

After an informed discussion about his options and the side effects of the cancer treatments, he and his physician decided to postpone the treatment. He made the trip to Hawaii with his family, then returned to start cancer treatments, the study said.

"Patients don't see the relevance of an advance directive," said Periyakoil. "They do see the relevance of a bucket list as a way to help them plan ahead for what matters most in their lives."

Eric Neri, a research data analyst, and Helena Kraemer, PhD, professor of biostatistics, are co-authors of the study.

Stanford's Department of Medicine and the Veterans Affairs Palo Alto Health Care System supported the research. **ISM**

OF NOTE

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

Shipra Arya

Eran Bendavid

David Camarillo

Gerald Grant

Gary Darmstadt

Brooke Howitt

Michael Howitt

SHIPRA ARYA, MD, was appointed associate professor of surgery, effective Jan. 1. In addition, she was awarded the 2017 S. Timothy String President's Award by the Southern Association for Vascular Surgery. The honor, which recognizes the best paper on vascular surgery presented at the association's annual meeting, was given for the paper "High hemoglobin A1C associated with increased adverse limb events in peripheral arterial disease patients undergoing revascularization," of which she was lead author. In addition, she was named a co-chair of the leadership committee of the Association of Academic Surgery.

ERAN BENDAVID, MD, was promoted to associate professor of medicine, effective Dec. 1. His work uses empirical and modeling approaches to study the impacts of changing economic, political and natural environments on the major causes of death and disability in resource-strapped regions.

DAVID CAMARILLO, PhD, assistant professor of bioengineering, and **GERALD GRANT**, MD, associate professor of neurosurgery, have received a $1 million, four-year grant from the National Institute of Neurological Disorders and Stroke to develop and share approximately 1,000 mouthguard sensors with head-injury researchers nationwide. That will allow for the collection of additional data, in collaboration with other researchers, to investigate the effect of head impacts on brain health.

GARY DARMSTADT, MD, professor of pediatrics and associate dean for maternal and child health, has received a $2 million grant from the Bill and Melinda Gates Foundation to determine the gestational age and preterm birth rates in low-resource settings using newborn metabolic profiles. In addition, he has received a $2 million grant from the United Arab Emirates to support a forthcoming *Lancet* series focused on building evidence on how transforming gender norms can improve health outcomes.

BROOKE HOWITT, MD, was appointed assistant professor of pathology, effective Dec. 1. Her research focuses on classifying and evaluating neoplasms of the female genital tract.

MICHAEL HOWITT, PhD, was appointed assistant professor of pathology, effective Dec. 1. His research explores the relationship between intestinal tuft cells, the immune system and microorganisms. His work aims to expand therapeutic options for treating gastrointestinal inflammatory disease.

JAMES KORNDORFFER JR., MD, was appointed associate professor of surgery and vice chair of education for the Department of Surgery, effective Dec. 1. His research focuses on using technology, including simulation, to improve teaching and training in the field of surgery.

CATHERINE KRAWCZESKI, MD, was promoted to professor of pediatrics, effective Dec. 1. Her research focuses on the outcomes of critically ill pediatric heart patients after cardiopulmonary bypass. She directs the pediatric cardiology fellowship and is the medical director of cardiovascular intensive care at Lucile Packard Children's Hospital Stanford.

PARAG MALLICK, PhD, was promoted to associate professor (research) of radiology, effective Jan. 1. His research uses multiscale systems approaches to accelerate diagnostics and personalized medicine.

LATHA PALANIAPPAN, MD, professor of medicine, received a health leadership award from the India Community Center in Milpitas, California, for her work on understudied populations in medicine and her efforts to encourage these communities to participate in clinical research. Her research focuses on the effects of physical activity on the management of diabetes, particularly in Asian populations, which have higher rates of diabetes.

THEO PALMER, PhD, was promoted to professor of neurosurgery, effective Jan. 1. His research examines how neural stem cells respond to genetic and environmental factors, and how these responses influence the integration of newly generated neurons into functional neural circuits. Specifically, he examines neurodevelopmental disease risk genes that can become problematic when combined with an illness experienced by the mother during pregnancy.

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, was awarded a 2018 Vilcek Prize for Creative Promise in Biomedical Science. The honor, which recognizes young immigrants who have demonstrated exceptional promise early in their careers, includes a $50,000 cash award. He received the prize for developing realistic models of the human brain and unearthing fundamental insights into the biology of neuropsychiatric diseases like autism.

ALAN SCHATZBERG, MD, the Kenneth T. Norris Jr. Professor of Psychiatry and Behavioral Sciences and director of the Stanford Mood Disorders Center, received a 2017 Julius Axelrod Mentorship Award from the American College of Neuropsychopharmacology. The honor is given to a college member who has made an outstanding contribution to neuropsychopharmacology by mentoring and developing future leaders.

VITTORIO SEBASTIANO, PhD, assistant professor of obstetrics and gynecology, received a $100,000 research grant from the American Federation for Aging Research. The awards are given to early career investigators to support research on aging and age-related diseases. His project will investigate aging reversal in cells using transient reprogramming.

MEHRDAD SHAMLOO, PhD, was promoted to professor (research) of neurosurgery, effective Dec. 1. His work focuses on understanding normal and pathological brain functions in neurological disorders, such as stroke, Alzheimer's disease and autism, and on developing experimental therapeutics.

TAIT SHANAFELT, MD, was appointed professor of medicine, effective Nov. 1. His clinical work and research focus on the treatment of patients with chronic lymphocytic leukemia and other low-grade lymphoid leukemias. He is Stanford Medicine's chief wellness officer and directs the WellMD Center.

CARLA SHATZ, PhD, the Sapp Family Provostial Professor, David Starr Jordan Director of Stanford Bio-X and a professor of neurobiology and of biology, is a winner of the 2017 Harvey Prize in Science and Technology. The $75,000 prize recognizes individuals who have made significant contributions to humankind. She is being honored for her discoveries about the development of visual circuits in the brain.

SIDHARTHA SINHA, MD, was appointed assistant professor of medicine, effective Dec. 1. His research focuses on understanding the microenvironmental changes in the inflamed versus normal gut, with the goal of identifying therapeutic targets for people with gastrointestinal immune-mediated disorders. He also uses machine learning to understand patient and societal perceptions related to gastrointestinal diseases on social media and in other unstructured data sources.

DAVID SPAIN, MD, professor of surgery, the David L. Gregg, MD, Professor and chief of trauma and critical care surgery, has received a four-year, $2.5-million grant from the National Institute on Minority Heath and Health Disparities. The grant will allow Spain, along with Eve Carlson, PhD, from the U.S. Department of Veterans Affairs, to develop and test a screen to accurately identify people, including members of several minority groups, at high risk for mental health problems following serious illnesses or injuries.

GARY STEINBERG, MD, PhD, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences and chair of neurosurgery, has received an American Ingenuity Award in life sciences from *Smithsonian* magazine. The honor recognizes outstanding innovators in a variety of fields. His work uses stem cell transplants to the brain to help stroke patients recover neurologic functions, even years following a stroke.

DAVID K. STEVENSON, MD, the Harold K. Faber Professor of Pediatrics and senior associate dean for maternal and child health, has been elected a fellow of the American Association for the Advancement of Science. He was selected for distinguished contributions in neonatology and pediatrics, particularly for his work on neonatal jaundice, bilirubin production and heme oxygen biology. His clinical and research focus is on neonatal jaundice and the prevention of preterm birth.

SEDA TIERNEY, MD, was appointed associate professor of pediatrics, effective Dec. 1. She directs the Pediatric Vascular Research Laboratory and is the director of research for the noninvasive imaging laboratory at Lucile Packard Children's Hospital Stanford. Her research focuses on noninvasive assessment of vascular health in children and the use of telehealth to deliver interventions to improve cardiovascular health.

JONG YOON, MD, was promoted to associate professor of psychiatry and behavioral sciences, effective Oct. 1. His research focuses on developing new treatments for schizophrenia and psychosis by examining the neural mechanisms driving the conditions. **ISM**

James Korndorffer Jr.

Catherine Krawczeski

Parag Mallick

Latha Palaniappan

Theo Palmer

Sergiu Pasca

Alan Schatzberg

Vittorio Sebastiano

Mehrdad Shamloo

Tait Shanafelt

Carla Shatz

Sidhartha Sinha

David Spain

Gary Steinberg

David K. Stevenson

Seda Tierney

Jong Yoon