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. In the study, Levy and his team injected two immune-stimulating agents directly into solid tumors.

Studying mice, the researchers found that Levy’s method works to reactivate the cancer-destroying rangers, or activated T cells, which have been otherwise unable or uninterested in finding and destroying the cancer. The 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.

“This is a major advance,” said Levy, who holds the Robert K. and Helen K. Summy Professorship in the School of Medicine.

In this field, the hard part is usually developing a reagent that stimulates the immune system to attack a tumor. Once you have that, you can do a lot with it. The hard part is usually making it specific to the tumor. The unique aspect of our approach is that it works much, much better than that.”

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.

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 by reactivating 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-stimulating agents 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.

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Eventually engineered to spontaneously develop breast cancers in all 10 of their mammary glands, 87 of 90 mice were cured. In the mice, the tumors again regressed after a second treatment. The researchers saw similar results in mice bearing breast, colon and melanoma tumors.

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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.

*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,” 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.

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.”

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

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 WASH interventions or a control group. The six clusters were not randomized but grouped according to geographic clusters of Bangladesh after two years. The mothers were randomly assigned to one of the WASH 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; and WASH and nutritional supplements.

After two years, nearly all the interventions improved child growth and were implemented in many communities around the world, but they were not rigorously tested.

“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 were not measurably taller and were less likely to die during the study, but WASH interventions alone did not improve growth.

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 of the WASH 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; and WASH and nutritional supplements.

After two years, nearly all the inter-ventions reduced diarrhea. Although ex-pected, the result is important because it suggests that families did adhere to the interventions. It’s important to 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 nutrition was the most effective at reducing diarrheal disease. Sanitation and combined water, sanitation and handwashing interventions had the greatest effect on child mortality, in addition to improving growth. Children receiving this intervention were 38 percent less likely to die compared to children in the control group.

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

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This was entirely unexpected and surprising.”
A physician for Team USA: Eugene Roh

Eugene Roh has been the orthopaedic surgeon for the United States Olympic Team since 1988, when he began his career as a physician for the U.S. Olympic Training Center in Colorado Springs. Roh has treated athletes in the Summer Olympics since 1996, and has worked at the Winter Olympics since 2002. He has treated athletes in the 2018 Winter Games. Roh is an expert in sports medicine and treats patients in the School of Medicine's sports medicine clinic, 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 am 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.

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

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.

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 brings the largest group of athletes to the games. But I will be working as a liaison between both medical teams.

The research was supported by the Bill & Melinda Gates Foundation, Stanford's Department of Medicine also supported the research.

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 new Center for Innovation in Global Health.

Co-authors of the publication include scientists from Stanford's Institute for the Study of the Developing World, the University of Washington, the University of California, 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.

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 Scan 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 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-sensing 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 Al-exander Yu, MD, MPH, clinical fellow in infectious diseases.
• “Mental health issues and violence among adolescents in the Nakhon Phanom province, Thailand: How does community-based programming prevent or mitigate both?” — Clea Sarnquist, PhD, MPH, senior research scholar and lecturer in the School of Public Affairs, and Michael Biancochi, MD, assistant professor of medicine.
• “Linguistic and cultural adaptation of the Build- ing Empowerment and Resilience Program for adolescent girls in Gujarat, India” — Jennifer Keller, PhD, clinical associate professor of psychiatry and behavioral sciences.

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. Willmann 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 eaglegill@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.

As a boy growing up in South Korea, Eugene Roh traveled to Seoul in 1988 to attend the Summer Olympics. He is an expert in sports medicine and treats patients in the Stanford Orthopedic 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 injuries using ultrasound and regenerative medicine. Recently, writer Grace Hammersmrt got a chance to ask him some questions about his interest in the Olympics and working with athletes. Stanford's Department of Medicine also supported the research.

Continued on page 4
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 spread.

Now, researchers at the School of Medicine have identified a link between changes in the cancer cells’ internal scaffolding and the development of drug resistance. This finding could pave the way for new treatments for basal cell carcinomas.

The researchers found that blocking this connection using an inhibitor prevents the cancer cells from developing resistance to treatment. The mechanism by which this happens is still being investigated, but it highlights the potential 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 draw to become micrometastatic in the body, even if their genes don’t depend on genetic mutations often associated with the disease."

Most common cancer in U.S.

A paper describing the research was published 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 impressing proteins 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, sending signal copies 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. Step one of 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 Smoothen- ined 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

Joseph Woo takes on the challenge of repairing aortic valves

By Ruthann Richter

Nathan Healey was in the prime of his life, a ten- nis 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 what 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 Univer- sity 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 deci- sion: 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.

He decided to take the extraordinary step of re- pairing the valve and perform a creative trimming and sculpting. He cut out one of the oddly shaped flaps and used that tissue to fashion two flaps of equal size. He also rebuilt some of the surrounding heart muscle 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, a process that 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 require patients 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 work well but aren’t as durable, par- ticularly when used in younger patients, who have more vigorous 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. Multi- ple studies have shown that patients who undergo mi- tral valve repair do better overall. They are more likely to survive, spend less time in the hospital, and suf- fer fewer complications, such as infection and stroke, compared with those who receive substitute valves, whether animal or mechanical. The mitral valve con- trols the flow of blood from the left atrium into the left ventricle.

Fixing the aortic valve

While mitral valve repair has gained greater accep- tance, 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 aor- tic 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.

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 pre- serve 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 per- form 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-
clarding 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 a screen and an annotated display, showing a 3D model of the valve and its surrounding structures. The team then removed the defective valve, then meticulously removed the aortic valve tissue from the diseased valve. They replaced the aortic valve with a cannula, which was 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.

Although this was a technically difficult procedure, it was performed without incident. I was very lucky to get the surgeon, and I was lucky to get the opportunity.”

All-repair philosophy

In general, Woo said he likes to approach each patient as a potential candidate for repair, rather than replace. He uses an all-repair philosophy, 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 every patient with an all-repair philosophy,” he said. “No one should be viewed as automatically not a candidate. Everyone should have an opportunity.”

He said he often goes talk to cardiology 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,” he 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 mara- thon repair procedure after spending 10 days in the hospital. Woo implanted a pacemaker in his heart, as the rupture had temporarily stopped the heart, then re- sumed to turn it on. Understanding this new connection between the cytoskeleton, and cellular scaffoldings, that helps cells maintain their shape and govern their rigidity.

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 financial 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 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 Cy- berKnife radiotherapy and localized surgery.

Given these factors, Vagelos, a professor of cardiovascualr 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 Adminis- tration in 2012 for use in patients who, like Hosking, were not good candidates for traditional aortic valve replacement, or TAVR. The procedure is immensely grateful to her medical team.

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 liv- ing,” 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.”

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

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

A new heart was implanted in the patient’s aortic valve, leaving the patient with one functioning valve. The aortic valve opening was narrowed, which restricted blood flow through the heart.

The new valve was compressed into a thin catheter, which was inserted into a blood vessel in the leg, then threaded up through the aorta and into the heart. The new valve was 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. She was 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 who are not candidates for open-heart surgery, suggesting that it is a valuable alternative to currently available treatments.

“TAVR is considered by many in the field as a game-changer,” said John V. Goronzy, PhD, professor of dermatology Jean Tang, MD, PhD; and associate professor of dermatology Sumaira Aasi, MD; assistant professor of dermatology Tyler Holling, MD; clinical professor of dermatology Sumeet Saini, MD; clinical professor of dermatology Jean Tang, MD, PhD.

The research was supported by the National Institutes of Health, a Re- search training grant and the Damon Runyon Cancer Research Foundation.

Oro has received funding from Novartis, Stanford’s Department of Dermatology also supported the work. 
Bloodless

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 the procedure. “We were happy there was a solution, but when they said ‘transfusion,’ my heart dropped.”

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.

“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 planned every step of Lola's care to minimize blood loss, monitoring her blood cells carefully and picking surgical techniques and materials with minimal blood loss in mind.

Hanley and pediatric cardiothoracic surgeon Karin L. Hanley, MD, clinical associate professor of pediatrics, said 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 cardiothoracic surgeon who cared for Lola.

Tweak to assay could bolster disease detection, according to researchers

By Hanae Armitage

A team of School of Medicine researchers said they have developed a technique that could help them more precisely detect diseases or disorders such as cancer or a heart attack in the future.

The technique is an improved method to detect some biomarkers — protein signals in blood or tissues that Vorlengh said may increase patients' risk of inflammation, and some data suggests patients that 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 for both medical reasons and to accommodate patients' religious beliefs.

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 agreed to allow the procedure, their 7-month-old baby was born has less blood to begin with. Compared to a full-term baby, a premature baby has less blood to begin with. In the past, the problem has been solved by transfusing blood. For Lola, the Packard Children's team took a different approach.

The technique, a modified assay, called circu- lus or even to head off the development of metastases or lingering cancer cells, even if the parents disagree. When they agreed to allow the procedure, their 7-month-old baby was born has less blood to begin with. Compared to a full-term baby, a premature baby has less blood to begin with. In the past, the problem has been solved by transfusing blood. For Lola, the Packard Children's team took a different approach.

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A gift of $9.5 million will launch the Taub and Dianne Taube Youth Addiction Initiative, a program that aims to comprehensively address the treatment and prevention of addiction during ad- oleescence 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 collabora- tion with TeachAids, a Stanford-funded 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 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 Mi- nor, MD, dean of the School of Medi- cine. “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 comprehensive interven- tion efforts during these formative years.

The Taub and Dianne Taube Youth Addiction Initiative will be led by the Division of Child and Adolescent Psychiatry in the Department of Psych- iatry and Behavioral Sciences, which has identified advancing the understand- ing 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 earlier 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 stig- mated issue both in adults and in the general population. Adolescence is a particularly vulner- able time, with hormonal surges and changes in brain development occurring just as young people are facing major life decisions and responsibilities at home and in school, and drug use frequently overlaps with other mental health conditions such as depression and anxiety. Al- though 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 Taub’s gift will establish an en- dowed directorship to organize, launch and lead the youth addiction initiative; an endowed postdoctoral fellowship to train an early career researcher or cli- nician in child and adolescent mental health; a focused youth addiction; and endowed faculty scholar awards for three faculty members who will, respec- tively, 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 to children, parents and coaches to trivialize these head injuries and fail to allow the athlete to continue playing, which prolongs recov- erty time and increases the risk of a follow-on concussion.

The Taubes’ gift to launch the Taube Stanford Concussion Collaborative will en- able Gerald Grant, MD, associate profes- sor of neurosurgery; David Camarillo, PhD, assistant profes- sor of bioengineering; and Piya Sorcar, PhD, 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 fel- low parents about the safety of youth athletes in our community and beyond,” said Dianne Taube. “Our hope through this initiative is to educate our youth and provide current, useful infor- mation to educate parents, coaches and players.”

Grant and Camarillo have already made strides in more precisely measur- ing of children and adolescents. The Tad and Dianne Taube of Taube Philan- thropies have made two gifts totaling $14.5 million to launch Stanford initiatives addressing youth addiction and children’s concussions.

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 major- ity of respondents had not 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 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 “career” 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 a goal-related personal goal, such as running a marathon; 51 percent included achieving a life milestone, such as a 50th wedding anniversary; 50 percent included spending quality time with family and friends; 24 percent valued increase in social stabil- ity; and 15 percent included a daring activity.

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

Past research has found that when doctors talk to patients about their mortality, it affects those whose situation is terminal — but not those with chronic or terminal ill- nesses — about the patients’ goals to help encourage a vital part of the advance-care planning process. But it’s often awkward to have these conver- sations, particularly when they are about the end of life, the study said.

gamma 7

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 under- standing 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 peo- ple are far more open to talking about what 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 dis- cussing what the patient’s goals are, the best possible care plan can be laid out, she said.

“When we talk, it’s about life,” Periya- koil said. “We talk about what’s going on in the cancer, but he was really stressed because he wanted to take his family to Hawaii but had treatment sched- uled. 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 cancer treatments, he and his physician decided to postpone the treatment. He made the trip to Hawaii with his family, then re- turned to start cancer treatments, the study said.

“Patients don’t see the relevance of an advance di- rective,” 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 Krae- mer, PhD, professor of biostatistics, are co-authors of the study.

Stanford’s Department of Medicine and the Veteran- ans Affairs Palo Alto Health Care System supported the research.

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 concusions — two of the most sig- nificant issues af- ceiling the health and well-being of children and adolescents.

A gift of $9.5 million will launch the Taub 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.

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Grant and Camarillo have already made strides in more precisely measuring addiction, diagnosing and treating concussions in children with gait BlackAids 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.

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SHIPA 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 worse outcomes in 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.

GARY DARMASTAD, 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 biometric 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 explores the relationship between intestinal tuft cells, the immune system and microorganisms. Her work aims to expand therapeutic options for treating gastrointestinal inflammatory disease.

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

LATINA PALANIPAN, 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.

SERGIO PASCA, MD, assistant professor of psychiatry and behavioral sciences, was awarded a 2018 Vylek 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 and aging.

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 award is 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 pathologically brain functions in neurological disorders, such as Alzheimer’s disease, schizophrenia and autism, and on developing experimental therapeutics.

TAIT SHANAEFT, MD, was appointed assistant professor of medicine, effective Dec. 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.

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.

DANIEL WEAVER, PhD, professor of pediatrics and senior associate dean for maternal and child health, has been elected a fellow of the American College of Neuropsychopharmacology. The honor 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.

JONG YOON, MD, was appointed 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.