INSIDE STANFORD MEDICINE

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High-resolution images of more than 150-year-old anatomical wax models are being used as a teaching tool.

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Human cord blood gives old mice an edge

By Bruce Goldman

Human umbilical cord blood can rejuvenate learning and memory in older mice, according to a study by researchers at the School of Medicine.

The researchers identified a protein, abundant in human cord blood but decreasingly so with advancing age, that had the same effect when injected into the animals.

The findings could lead to new treatments for age-associated declines in mental ability.

"Neuroscientists have ignored it and are still ignoring it, but to me it's remarkable that something in your blood can influence the way you think," said the study's senior author, Tony Wyss-Coray, PhD, professor of neurology and neurological sciences and a senior research career scientist at the Veterans Affairs Palo Alto Health Care System. The lead author is former postdoctoral scholar Joseph Castellano, PhD, who is now an instructor of neurology and neurological sciences.

The study was published online April 19 in *Nature*.

In a widely discussed earlier study, Wyss-Coray's lab showed that direct infusion of young mice's plasma, the cell-free portion of blood, benefited old mice. Those benefits extended beyond biochemistry and physiology to actual performance on tests of memory and learning, the researchers found.

The new study marks the first demonstration that human plasma can aid older mice's memory and learning, which both Wyss-Coray and Castellano said would seem to increase the likelihood that it could have a similar beneficial effect in people. It's also promising from a drug-development standpoint, they suggested, that a single protein appears largely capable of mimicking those benefits.

Age-associated changes in blood

Comparing blood plasma from 19- to 24-year-olds, 61- to 82-year-olds and umbilical cords, researchers identified age-associated changes in a number of proteins.

These changes, the investigators suspected, might affect a brain structure called the hippocampus, which in both mice and humans is critical for converting experiences into long-term memories. In particular, the hippocampus is essential for helping you remember spatial information, such as how to find your way back to the car you parked in a multilevel structure several hours ago, and information about autobiographical events, such as what you ate for breakfast.

For largely unknown reasons, the hippocampus is especially vulnerable to normal aging, said Wyss-Coray. "With advancing age, the hippocampus degenerates, loses nerve cells and shrinks," he said. The capacity to learn and remember falters in lockstep. Hippocampal deterioration is also an early manifestation of Alzheimer's disease.

To distinguish the effects of old, young and "youngest" human blood on hippocampal function, the researchers used immune-deficient laboratory mice that could be given repeated injections of human plasma without experiencing negative immune reactions. Experiments undertaken before injecting human plasma into the mice showed that, like their immune-competent peers, these mice's hippocampal activity, integrity and regenerative capacity dropped off in old age — indeed, a bit faster.

Old immune-deficient mice performed more poorly than younger ones on tests of memory and learning. One such test, the Barnes maze, employs a table, about 4 feet in diameter and 1.3

See BLOOD, page 7

NORBERT VON DER GROEBEN

Tony Wyss-Coray and his team identified a protein in human umbilical cord blood that revitalized memory and learning ability in older mice.

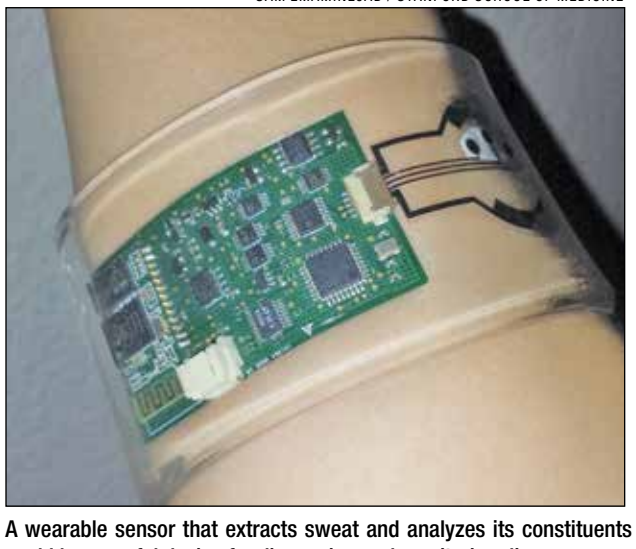
Wearable sweat sensor holds promise for diagnosing cystic fibrosis, other diseases

By Jennie Dusheck

A wristband-type wearable sweat sensor could transform diagnostics and drug evaluation for cystic fibrosis, diabetes and other diseases.

The sensor collects sweat, measures its molecular constituents and then electronically transmits the results for analysis and diagnostics, according to a study led by researchers at the School of Medicine, in collaboration with UC-Berkeley. Unlike old-fashioned sweat collectors, the new device does not require patients to sit still for a long time while sweat accumulates in the collectors.

SAM EMAMINEJAD / STANFORD SCHOOL OF MEDICINE



A wearable sensor that extracts sweat and analyzes its constituents could be a useful device for diagnosing and monitoring diseases.

"This is a huge step forward," said Carlos Milla, MD, associate professor of pediatrics at Stanford.

The study was published online April 17 in the *Proceedings of the National Academy of Sciences.* Milla shares senior authorship with Ronald Davis, PhD, professor of biochemistry and of genetics at Stanford. Former Stanford postdoctoral scholar Sam Emaminejad, PhD, is the lead author.

How does it work?

The two-part system of flexible sensors and microprocessors sticks to the skin, stimulates the sweat glands and then detects the presence of different molecules and ions based on their electrical signals. The more chloride in the sweat, for example, the more electrical voltage is generated at the sensor's surface. The team used the wearable sweat sensor in separate studies to detect chloride ion levels — high levels are an indicator of cystic fibrosis — and to compare levels of glucose in sweat to that in blood. High blood glucose levels can indicate diabetes.

See SENSOR, page 6

Genetic counseling could help prevent unnecessary double mastectomies

By Krista Conger

A recent survey of over 2,000 women newly diagnosed with breast cancer found that half of those who undergo bilateral mastectomy after genetic testing don't actually have mutations known to confer increased risk of additional cancers, according to a study by researchers at the School of Medicine and four other U.S. medical centers.

Allison Kurian

Instead the women had what are known as variants of uncertain significance, or VUS, that are often eventually found to be harmless. A bilateral mastectomy is a surgical procedure in which both of a woman's breasts are removed after a diagnosis of cancer in one breast.

The finding highlights the need for genetic counselors to help both patients and physicians better understand the results of genetic testing intended to determine a woman's risk for cancer recurrence or for developing a separate cancer in her ovaries or unaffected breast.

See MASTECTOMY, page 6

Suppressing protein extends life of mice with ALS-like disease

By Jennie Dusheck

A study led by researchers at the School of Medicine has revealed a possible new therapeutic approach for amyotrophic lateral sclerosis, a progressive neurodegenerative disease.

The Stanford-led team performed a series of experiments showing that suppressing a certain protein in a mouse model of ALS, or Lou Gehrig's disease, could markedly extend the animal's life span. In one experiment, none of the untreated mice lived longer than 29 days, while some of the treated mice lived more than 400 days.

A paper describing the work was published online April 12 in *Nature*. The paper — by senior author Aaron Gitler, PhD, associate professor of genetics, and lead author Lindsay Becker, a graduate student — details a series of experiments that together suggest a possible strategy for treating ALS.

Finding a different approach

ALS is a disease in which the nerve cells in the brain and spinal cord degenerate, leading to wasting of the muscles. Patients gradually lose the ability to move, speak, eat or breathe, often leading to paralysis and death within two to five years.

ALS is inherited in an estimated 5-10 percent of cases. In the remaining cases, the cause is unknown.

Exactly how ALS works is still poorly understood, but knowing which genes are involved can point researchers toward processes inside cells that would be good targets for drugs.

One indicator of ALS, as well as other neurodegenerative diseases, is clumps of protein in the brain. In ALS, these clumps, or aggregates, are made up of a protein called TDP-43. Eliminating TDP-43, and therefore the TDP-43 aggregates, might seem like a good way to prevent or cure ALS. But cells need TDP-43 to survive, so suppressing TDP-43 itself is not a good idea.

A different approach was needed. The researchers knew that a second protein, ataxin 2, helped cells survive when TDP-43 formed toxic clumps. Unlike TDP-43, ataxin 2 is not essential for a cell's survival, making it a reasonable therapeutic target, Gitler said.

In a previous study, the Stanford-led team had shown that when ataxin 2 is suppressed or blocked in yeast cultures and fruit flies that carry the human TDP-43 gene, cells are more resistant to the potential toxic effects of the clumping TDP-43 protein.

In still another study, Gitler and his colleagues had shown that versions of the human ataxin 2 gene that resulted in a more stable ataxin 2 protein — and therefore more of the protein — increased the risk for developing ALS. The researchers reasoned that if mutations that increased the amount of ataxin 2 raised the risk of ALS, maybe lowering the amount of ataxin 2 would protect a person from ALS.

Becker used genetically engineered mice whose neurons produced human TDP-43 protein at high levels. These mice exhibit some features that resemble human ALS, including a buildup of clumps of TDP-43 in their neurons. These mice also have difficulty walking and typically have life spans of no more than 30 days.

A preventive that worked in mice

"We wanted to find out if we could protect these mice from the consequences of TDP-43 by lowering the amount of ataxin 2," said Gitler. Becker genetically engineered these ALS mice to have half the normal amount of ataxin 2, and also engineered other mice to completely lack the protein. She found that with half the ataxin 2, the ALS-like mice survived much longer. "But what was really astounding," said Becker, "was that when we completely removed ataxin 2, there was really an unprecedented survival; some of the mice lived hundreds and hundreds of days."

Gitler's team next tried something that could have a more direct therapeutic value: treating mice with a type of DNA-like drug, designed to block the production of ataxin 2. These so called "antisense oligonucleotides" are strands of synthetic DNA that target a gene and block the expression of the protein that it encodes. Delivery of the antisense oligonucleotides to the nervous systems of some of the ALS mice enabled them to maintain their health much longer than the ALS mice treated with a placebo.

PAUL SAKUMA

Aaron Gitler and his colleagues found that suppressing a protein in mice genetically engineered to have an ALS-like disease allowed them to live longer and improved their motor function.

A similar antisense oligonucleotide was recently approved for safety trials in pediatric patients with spinal muscular atrophy, and other antisense oligonucleotides have passed safety trials — factors that Gitler said give him hope for a similar strategy for ALS.

Becker said the study showed that suppressing ataxin 2 delayed onset and slowed the progression of the ALS-like disease in mice that were not yet showing symptoms. Whether oligonucleotides or other protein-blocking treatments could reverse symptoms in mice that are already sick is another question. "That's the next set of experiments that we are working on," she said. Because TDP-43 clumping occurs in nearly all ALS cases, targeting ataxin 2 could be a broadly effective therapeutic strategy, she said.

Other Stanford-affiliated co-authors are postdoctoral scholar Brenda Huang, PhD; graduate student Gregor Bieri; research assistant Rosanna Ma; and postdoctoral scholar David Knowles, PhD.

Researchers from St. Jude Children's Research Hospital, Goethe University Frankfurt, the University of Utah, Howard Hughes Medical Institute and Ionis Pharmaceuticals also contributed to the study.

The research was supported by the National Institutes of Health, the National Science Foundation, the Robert Packard Center for ALS Research at Johns Hopkins, Target ALS, the Glenn Foundation and the German Research Foundation.

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

Big Data in Biomedicine Conference set for May 24-25

By Jennie Dusheck

The 2017 Big Data in Biomedicine Conference, set for May 24-25 at the School of Medicine, will explore success stories of and opportunities for harnessing big data for both research and clinical care.

This year's meeting, titled "Big Data in Biomedicine: Transforming Lives Through Precision Health," will focus on precision health in action, highlighting the Precision Medicine Initiative, the Chan Zuckerberg Initiative and other promising new initiatives.

"We're living in a time of unprecedented complexity — and historic opportunity," said Lloyd Minor, MD, dean of the School of Medicine, who will give introductory remarks at the conference. "Big data, artificial intelligence and other technological breakthroughs enable us to fulfill our promise to predict, prevent and cure — precisely — on a global scale."

Last year's event brought more than 500 attendees to the campus, while another 2,000 watched online via live-streamed video. This year, the conference, which debuted in 2013, is expected to once again draw hundreds of researchers and leaders from academia, health care, government and industry. Presenters will discuss the National Institutes of Health Precision Medicine All of Us research program; NIH's National Library of Medicine; and the Chan Zuckerberg Initiative.

Driver of precision health

Biomedical data comes from diverse sources, including millions of electronic health records, wearable sensors and biomedical databases. Searching hundreds of millions of de-identified personal medical records — for relationships among diseases, treatments and outcomes — can quickly reveal new avenues for clinical research. The cutting-edge approach can point to previously unsuspected opportunities for treatment as well as opportunities to improve patient care. It's one of the drivers of precision health at Stanford Medicine, whose goal is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

But the big data approach means repurposing data collected for other uses, most often for diagnostics and billing. Utilizing such data means solving myriad challenges, such as standardizing the metadata that characterizes each data set and finding better ways to make databases accessible to researchers.

Topics this year include recent big data success stories connected to cancer, cardiovascular disease and clinical trials; new opportunities for taking advantage of big data; the interface between regulatory science — the study of the science of regulating research and development —and data science; the interface between artificial intelligence and interpretation of biomedical imaging; and network science, including, for example, how to analyze complex relational data in biological data or social data.

This year's speakers will include Marc Tessier-Lavigne, PhD, president of Stanford; Stephen Quake, professor of bioengineering at Stanford; Jennifer Van Eyk, MD, professor of medicine at Cedars-Sinai Medical Center; Russ Altman, MD, PhD, professor of bioengineering, of genetics and of medicine at Stanford; Michelle Rohrer, PhD, senior vice president and global head of product development regulatory and policy at Genentech Roche; Greg Moore, MD, PhD, vice president of Healthcare Google; Cori Bargmann, PhD, president of science for the Chan Zuckerberg Initiative; Nikesh Kotecha, PhD, vice president of informatics for the Parker Institute; Jessica Mega, MD, MPH, of Verily Life Sciences; and Nancy Brown, CEO of the American Heart Association.

To see the full list of speakers and register for the conference, visit http://bigdata.stanford.edu. **ISM**

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STANFORD MEDICINE

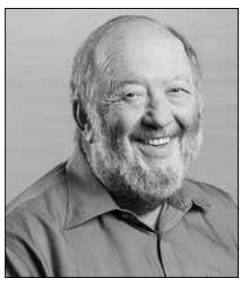
Fibrosis reversed when 'don't eat me' signal is blocked

By Krista Conger

Researchers at the School of Medicine have identified a pathway that, when mutated, drives fibrosis in many organs of the body.

The pathway underlies what have been considered somewhat disparate conditions, including scleroderma, idiopathic pulmonary fibrosis, liver cirrhosis, kidney fibrosis and more, the researchers found. These diseases are often incurable and life-threatening.

Importantly, the researchers were able to reverse lung fibrosis in mice by administering an antibody called anti-CD47 now being tested as an anti-cancer treatment.



Irving Weissman

"The variety of diseases caused by overproduction of fibroblasts has made finding a common root cause very challenging, in part because there has been no good animal model of these conditions," said Irving Weissman, MD, professor of pathology and of developmental biology. "Now we've shown that activating a single signaling pathway in mice causes fibrosis in nearly all tissues. Blocking the CD-47 signal, which protects cancer cells from the immune system, can also ameliorate these fibrotic diseases even in the most extreme cases."

The researchers hope their findings will lead to the development of a reliable treatment of many types of fibrotic diseases. They are also planning to investigate whether the anti-CD47 antibody could be an effective treatment for people with fibrosis.

A study describing the research was published online April 17 in the *Proceedings of the National Academy of Sciences*. Weissman, who directs Stanford's Institute for Stem Cell Biology and Regenerative Medicine and the Ludwig Center for Cancer Stem Cell Research and Medicine, is the senior author. Gerlinde Wernig, MD, assistant professor of pathology, is the lead author.

When injury response goes astray

Fibrosis occurs when the body's normal response to injury goes astray. An overenthusiastic or inappropriately timed proliferation of cells called fibroblasts, which make up the connective tissue surrounding and supporting all of our organs, can lead to many devastating diseases. Until now, it's not been clear whether these diseases share a common biological pathway.

The researchers were building upon previous work by Wernig on a condition called myelofibrosis, or fibrosis of the bone marrow. In a mouse model she developed, she had found that fibroblasts were producing unusually high levels of an important signaling molecule called c-Jun. C-Jun is a transcription factor that drives the production of many proteins involved in critical cellular processes. It's been implicated in many types of human cancer.

In the current study, Wernig investigated c-Jun expression levels in 454 biopsied tissue samples from patients with a variety of fibrotic diseases. She found that in every case the fibroblasts from the patients with fibrosis expressed higher levels of c-Jun than did control fibroblasts collected from people with nonfibrotic conditions.

"We found that c-Jun is not just overexpressed, but it's also highly activated," Wernig said. "We wondered if its activity is necessary to maintain the disease."

Blocking the expression of c-Jun in laboratory-grown lung fibroblasts collected from people with idiopathic pulmonary fibrosis substantially decreased the proliferation of these cells, but not of lung fibroblasts collected from people without fibrosis, Wernig said. Furthermore, mice genetically engineered to overexpress c-Jun in all their body's tissues developed fibrosis in nearly every organ, including lung, liver, skin and bone marrow. Finally, she also found an intriguing link to past work from the Weissman lab.

'A unifying mechanism'

"We found that c-Jun overexpression and over-activation is a unifying mechanism in many types of fibrosis," Wernig said. "But an even more exciting part of the story is the fact that we observed that the diseased, c-Jun-expressing fibroblasts are surrounded by immune cells called macrophages. This is reminiscent of what's often seen in human cancers."

Gerlinde Wernig

Over the past eight years, researchers in Weissman's laboratory have shown that many human cancers evade the immune system by expressing high levels of a protein called CD47 on their surfaces. Blocking this protein with an anti-CD47 antibody restores the ability of the macrophages to gobble the cancer and has proven to be a promising treatment in animal models of the disease. Anti-CD47 antibody is currently undergoing a phase-1 clinical trial in humans with advanced solid tumors.

"Like in cancer, these fibroblasts are proliferating excessively beyond what should be their natural limit," Weissman said. "We therefore wondered whether they are also expressing the 'don't eat me' signal on their surfaces to protect them from the immune system."

When Wernig treated mice with c-Jun-induced lung fibrosis with daily injections of anti-CD47 antibody, the animals exhibited significantly better lung function, lived longer than their peers and cleared the fibrosis.

The researchers plan to investigate whether any patients in the phase-1 trial of the anti-CD47 antibody also suffered from any fibrotic conditions. If so, they are eager to learn whether they experienced any relief as a result of participating in the trial.

"We have hit upon something unique in this study," Wernig said. "We identified a highly activated pathway that causes fibrosis in many tissues in mice, and we've showed that treating the animals with an anti-CD47 antibody reverses the fibrosis. We're hopeful that this could be a potential treatment for people with many types of fibrotic conditions."

Wernig also tested inhibitors of other genes activated by c-Jun in the abnormal fibroblastic cells, and inhibitors of two pathways also reduced the fibrotic lesions.

"This study shows once again how basic science investigations in one field can lead to advances in what appeared to be unrelated diseases," Weissman said. "Here, our studies of human cancer have led to the discovery of the mechanisms of how other 'dangerous' cells in fibrosis escape removal by the body's scavenger cells. It shows how important it is to develop appropriate animal models of human diseases and then to use those models to identify disease-specific pathways that can be targeted."

Weissman is the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research. He is a member of Stanford's Bio-X, Cardiovascular Institute and Cancer Institute.

Other Stanford co-authors are postdoctoral scholars Shih-Yu Chen, MD, PhD, and Lu Cui, PhD; former undergraduate student Camille Van Neste; graduate student Jonathan Tsai; professor of pathology Neeraja Kambham, MD; professor of pathology and of pediatrics Hannes Vogel, MD; professor of pathology Yaso Natkunam, MD, PhD; and professor of microbiology and immunology Garry Nolan, PhD.

The research was supported by the National Institutes of Health; the Department of Defense; the Food and Drug Administration; the Gates Foundation; the Virginia and D.K. Ludwig Fund for Cancer Research; the Stanford Cancer Institute; the Stanford Physician Scholar Society; the Institute for Immunity, Transplantation and Infection; Northrop-Grumman Corporation; Novartis; Pfizer; and Juno Therapeutics.

Weissman is the founder of Forty Seven Inc., which is exploring ways to use immunotherapy like the anti-CD47 antibody to fight cancer. A patent titled "Antifibrotic activity of anti-CD47 blockade" has been filed by the researchers.

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

At annual lab swap, one researcher's trash is another's treasure

By Jackie Flynn

Armed with spare pipettes, vials, centrifuges and chemicals, more than 150 people from across campus carted or carried their unneeded lab supplies to the lawn next to the Li Ka Shing Center for Learning and Knowledge on April 12 for the Office of Sustainability's third annual lab swap.

Throughout the day, scientists representing more than 100 labs sifted through the boxes and bins of lab equipment for unused or reusable materials worth thousands of dollars.

"A lot of these materials that would otherwise probably get thrown away don't end up in a landfill. Not just that, they get reused. They have a second life," said Rashmi Sahai, the assessments program manager at the Office of Sustainability, who helped organize the event.

Among the items for taking were laboratory staples such as ink cartridges, biohazard disposal kits, protein-extraction chambers, freezer racks, textbooks, hot plates, blenders and office chairs. A few gems of the past also emerged, including floppy disks, a Microsoft Windows 95 starter kit, filter paper estimated by the donor to be from the 1960s and cassette tapes from The Who and Steely Dan.

"We can give these items to someone who can use them, or we can just let them deteriorate," said Rebecca Agin, a life science technician and attendee at this year's swap. In addition to a variety of lab supplies, Agin brought several cases of wooden applicators that had been taking up shelf space in the lab where she works. "Being able to organize and contribute to sustainability is nice," she said.

Identifying a need

Stanford's campus includes about 2 million square feet of lab space, with about 5,000 research projects taking place at any given time. Research at that scale generates a significant amount of waste.

KURT HICKMAN

The Office of Sustainability's third annual lab swap, held April 12, was an opportunity for Stanford laboratories to get rid of unneeded equipment and reagents and also find stuff they need.

Trinidad Cisneros, a graduate student in immunology, was an intern in the Office of Sustainability when he came up with the idea for the lab swap. He said the event melds his interest in research with his love for the natural world.

"A lot of the items we use to conduct research are disposable, single-use items made out of some material that's recyclable, some of it that isn't. Seeing bags and bags of this pile up every day, you know, was heartbreaking," Cisneros said.

The event falls under the Office of Sustainability's Cardinal Green Labs program, which supports labs' reduction of waste, energy and water use across campus. The program offers services including free installation of energy-saving equipment timers and low-flow faucets, a biannual campus cleanup event and rebates for energy efficient low-temperature freezers.

When Cisneros envisioned the lab swap program in 2015, researchers were already sharing used equipment within lab networks, but there wasn't a centralized event for departments on campus. "We knew that there was a demand. We **See SWAP, page 5**

Photography helps children with chronic pain communicate and cope

By Erin Digitale

By the time she sees them, psychologist Anya Griffin's young patients have been in pain for months to years. In 2015, concerned that standardized questionnaires and 1-to-10 pain scales didn't give a personalized view of their struggles, Griffin, PhD, decided to try something different.

Then newly hired as clinical director of the Pediatric Rehabilitation Program at Stanford Children's Health's Center for Rehabilitation Services, Griffin borrowed an approach that originated in public health research: asking patients to take photos to convey their perspectives, a method called photovoice.

Many of Griffin's patients have complex regional pain syndrome, in which pain from an injury spirals out of control. The nervous system magnifies sensory input so that the lightest touch can cause fiery pain. Young people with the condition stop attending school, hanging out with friends, playing sports, taking music lessons, feeling like normal kids. The pain becomes its own disease.

Laura (a pseudonym) shows how she felt before (left) and after (right) undergoing rehabilitation for complex regional pain syndrome.

"I am not in their bodies and I can't possibly know what that experience is like," Griffin said. "I wanted to capture that so that I understand what they're experiencing and how it impacts their lives."

The photovoice project is supported by a seed grant from the School of Medicine's Medicine and the Muse program, which helped fund the purchase of cameras for patients to use. At the conclusion of the rehabilitation program — which lasts four to 12 weeks and includes medical evaluation and treatment, intensive physical and occupational therapy, and individual, group and family sessions with pain psychologists — Griffin has each patient pick a "before" and "after" photo and explain them. Here are two examples; a third is available online at http://stan.md/2kjZU8j.

Painting with her feet

"That was one of my very first days in the program," said Laura, 14, of the photo of herself making blue footprints. A dancer before she fractured her left foot at age 10, Laura (a pseudonym) had been in pain for three years by the time she started the pain rehabilitation program in May 2015. The pain had spread all the way to her left hip, leaving her unable to walk without a cane. Dancing, singing and other art forms she'd once loved had fallen out of her life.

Painting with her feet was kind of fun. "But I couldn't concentrate on the fun," Laura said. "I was just constantly making sure I wouldn't fall, focusing on the pain in my foot."

Lily (a pseudonym) depicted her life before (left) and after (right) rehabilitation for complex regional pain syndrome.

Partway through the program, Laura videotaped herself and several other patients dancing. "When I was having a really bad pain flare-up, I'd go back and watch that video," she saids. "I'd think, oh yeah, I can do this! The pain isn't everything. It isn't me."

By the time Laura's parents took her to her grandma's farm to celebrate her rehabilitation, she had progressed from walking without a cane to walking without a limp to running. With her complex regional pain syndrome in remission, she could also sit in the grass and feed her grandma's goats, which would have been impossible a few months earlier.

"In the second photo I was finally at peace with myself," she said. "I wasn't battling my foot."

Jagged edges

When she entered the rehabilitation program in May 2015, 15-year-old Lily (a pseudonym) had excruciating pain in her left leg and her right arm, the symptoms of 10 months of complex regional pain syndrome. She was in a wheelchair and taking so many medications that she has little memory of the period. "My life was shattered; there was no putting it back together," she said.

But with treatment, her life did come back together in a new way that she depicted in the second photo. "You can see it's even more beautiful with all the different pieces. If you hold it up to the light it shines through and has this beautiful mosaic effect."

Lily's mom remembers how her initial bewilderment at watching Lily break the blue glass in the photos gave way to new understanding. "She said, 'See all these jagged edges? That's the pain. It hurts, and nobody can touch me.' It put a new picture in my head of how bad it was for her." **ISM**

Single protein primes mouse stem cells to quickly repair injury

By Krista Conger

Like drag car racers revving their engines at the starting line, stem cells respond more quickly to injury when they've been previously primed with one dose of a single protein, according to a study from the School of Medicine.

Mice given the priming protein recover muscle function more quickly after damage, their skin heals more rapidly and even the shaved area around the injury regrows hair more quickly, the study found. Harnessing the power of this protein may one day help people recover more quickly from surgery or restore youthful vigor to aging stem cells.

"We're trying to better understand wound healing in response to trauma and aging," said Thomas Rando, MD, PhD, professor of neurology and neurological sciences. "We've shown that muscle and bone marrow stem cells enter a stage of alertness in response to distant injury that allows them to spring into action more quickly. Now we've pinpointed the protein responsible for priming them to do what they do better and faster."

Rando, who also directs Stanford's Glenn Center for the Biology of Aging, is the senior author of the study, which was published April 18 in *Cell Reports*. Former postdoctoral scholar Joseph Rodgers, PhD, is the lead author. Rodgers is now an assistant professor of stem cell biology and regenerative medicine at the University of Southern California.

Potential therapy

"Our research shows that by priming the body before an injury you can speed the process of tissue repair and recovery, similar to how a vaccine prepares the body to a fight infection," Rodgers said. "We believe this could be a therapeutic approach to improve recovery in situations where injuries can be anticipated, such as surgery, combat or sports."

Normally, adult, tissue-specific stem cells are held in a kind of cellular deep freeze called quiescence to avoid unnecessary cell division in the absence of injury. In a 2014 paper published in *Nature*, Rodgers and Rando showed in laboratory mice that an injury to the muscle of one leg caused a change in the muscle stem cells of the other leg. These cells entered what the researchers called an "alert" phase of the cell cycle that is distinct from either fully resting or fully active stem cells.

The fact that muscle stem cells distant from the injury were alerted indicated that the damaged muscle must release a soluble factor that can travel throughout the body to wake up quiescent stem cells. Rodgers and his colleagues found that a protein called hepatocyte growth factor, which exists in a latent form in the spaces between muscle cells and tissue, can activate a critical signaling pathway in the cells by binding to their surfaces. This pathway stimulates the production of proteins important in alerting the stem cells. But it wasn't known how HGF itself became activated.

Thomas Rando

In the new study, Rodgers and his colleagues identified the activating factor by injecting uninjured animals with blood serum isolated from animals with an induced muscle injury. (Mice were anesthetized prior to a local injection of muscle-damaging toxin; they were given pain relief and antibiotics during the recovery period.) After 2.5 days, the researchers found that muscle stem cells from the recipient animals were in an alert state and completed their first cell division much more quickly than occurred in animals that had received blood serum from uninjured mice.

Increased levels of a protein

"Clearly, blood from the injured animal contains a factor that alerts the stem cells," said Rando. "We wanted to know, what is it in the blood that is doing this?"

The researchers found that the serum from the injured animals had the same levels of HGF as the control serum. However, it did have increased levels of a protein called HGFA that activates HGF by snipping it into two pieces. Treating the serum with an antibody that blocked the activity of HGFA eliminated the recovery benefit of pretreatment, the researchers found.

In a related experiment, exposing the animals to a single intravenous dose of HGFA alone two days prior to injury helped the mice recover more quickly. They scampered around on their wheels sooner and their skin healed more quickly than mice that received a control injection. They also regrew their hair around the shaved surgical site more completely than did the control animals.

"Just like in the muscles, we saw the responses in the skin were dramatically improved when the stem cells were alerted," Rando said.

In addition to pinpointing possible ways to prepare people for surgeries or other situations in which they might sustain wounds, the researchers are intrigued by the role **See RANDO, page 5**

Digital archive of antique wax figures becomes a teaching tool

By Devika G. Bansal

Huddled over a virtual dissection table, Stanford medical students zoomed in on glistening muscles and nerves in the neck by swiping their fingers across the giant touchscreen designed to visualize an entire body in three dimensions.

What they were looking at, however, were not virtual renderings of human anatomy, or even images of the real thing; rather, they were examining high-resolution photographs of wax models made between the mid-17th and mid-19th centuries.

"We were shocked to know that they were real waxes," said Shayan Fakurnejad, a second-year medical student and teaching assistant in a clinical anatomy class where the digital images are used. "It is really interesting to be able to manipulate them in 3-D space."

Paul Brown, DDS, a consulting associate professor of anatomy at Stanford, led the effort of photographing about 200 of the more than 1,400 wax figures at La Specola, a natural history museum in Florence, Italy, in an effort to make them more accessible.

Most of the wax figures were created to demonstrate one body part or system, although some demonstrate more. A surgeon would dissect a body, and an artist would then cover the body part in plaster to create a mold. Then, the artist would pour colored wax into the molds, and add more detail by arranging silk threads to exactly reproduce capillaries and nerves. The workshop obtained corpses from a nearby hospital.

Without electricity, refrigeration or modern preservation techniques like embalming, the artists required roughly 200 cadavers to capture the minutiae of each wax figure. Two or three anatomists examined each sculpture before releasing it to the public.

"The amount of detail is astounding," Brown said. "They're actually the color you are inside, and they're anatomically precise." The wax figures have red muscles with accurate textures, yellow fat, twisting arteries and bluish veins. In contrast, a preserved cadaver is brown, he noted.

To help recreate depth perception, Brown's team took stereo images of the delicate wax figures. In addition, the team scanned some of the figures to create 3-D images using a technique called photogrammetry, which can reconstruct a model by stitching hundreds of pictures together, similar to the iPhone pan function.

The images have been used in a variety of courses as visual aids to enhance learning.

Steeped in history

"The Venus sculpture is stunning," said Brown, as he swiped through computer images of a wax model of a woman, reposing on a crimson silk bed. Her brown hair framed her face perfectly. She wore only a pearl necklace.

In the next image, the model's chest plate was off, revealing her rib cage, breast and the subcutaneous muscles.

JOHN GREEN

Paul Brown led the effort to photograph roughly 200 wax figures made between the mid-17th and mid-19th centuries.

JOHN GREEN

Students study images of the wax models in an anatomy class at Stanford. Most of the models were created to demonstrate one body part or system, although some demonstrate more.

The following images exposed her lungs, then her heart and uterus. Brown continued: "Look at the detail. Isn't that phenomenal?" The final layer of the anatomical Venus de Medici revealed the inside of her heart, as well as a fetus in her uterus.

La Specola, home of the Venus sculpture and other wax figures, is one of the oldest scientific museums in the world. Between 1775 and 1850, the museum was host to a wax modeling, or ceroplastics, workshop for the purposes of both art and medicine.

"The amount of detail is astounding."

"This is not a morbid collection," said Claudia Corti, a zoologist and curator of the wax collection at La Specola. "It's made for scientific public education. It came out during the Enlightenment period, when [artists] were trying to work precisely on a scientific basis."

Since its inception, the museum has attracted medical students and the general public alike. "Every once in a while, someone will faint," Brown said.

The waxes are still invaluable for people who want to take an elaborate look at how the human body is put together, Corti said.

Better than an app

Medical students agree. Although they dissect real cadavers, images of the waxes help illustrate anatomical features, said Karthik Nathan, another second-year medical student and teaching assistant. For example, real cadavers have a lot of connective tissue and layers of fat between the muscles, which makes it hard to distinguish at a fine level. The waxes, on the other hand, show clear muscle borders, Nathan said. "Also, some of the smaller arteries, veins and nerves are a lot more difficult to dissect," he said. "So having a 3-D representation of it is really useful."

The images help show a complete product if students don't have enough time to finish their dissections, Nathan added.

The waxes, students said, are also far better than the simulated images they access on an iPad app for anatomy. "The waxes look more realistic," said Jessica Plaza, an anatomy scholar who helps run the dissection lab. "They are more like a really good dissection, whereas the app is more computerized."

Brown credits the idea for the project to Robert Chase, MD, professor emeritus of surgery at Stanford, who came across the wax museum in the 1940s while stationed in Italy during World War II.

Brown hopes to annotate the digitized waxes to make for a richer experience. "Anatomy is really body geography — where is it and what do you call it," he said. With detailed notes, the waxes will offer a distinct edge over traditional methods of learning human anatomy, he said. **ISM**

Rando

continued from page 4

HGF and HGFA might play in aging. It's known that the pathway activated by these proteins is less active in older people and animals.

"Stem cell activity diminishes with advancing age, and older people heal more slowly and less effectively than younger people. Might it be possible to restore youthful healing by activating this pathway?" said Rando. "We'd love to find out."

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.

Rando is a member of Stanford's Bio-X, Neurovascular Institute and Cardiovascular Institute.

Other Stanford co-authors are former research assistants Matthew Schroeder and Chanthia Ma.

The research was supported by the National Institutes of Health, the Department of Veterans Affairs, The Donald E. and Delia B. Baxter Foundation and the Glenn Foundation for Medical Research.

Stanford's Department of Neurology and Neurological Sciences also supported the work. **ISM**

Swap

continued from page 3

knew that this behavior was already happening at a smaller scale," he said.

Tapping into something big

The initial lab swap event, held in conjunction with the School of Medicine, brought together over 100 labs and saved an estimated $100,000 in research-related costs. With that success, Cisneros and Sahai knew they had tapped into something big.

"Even as we were setting up our tables, people were bringing carts of items," Cisneros said. "Soon, we were just so busy that we couldn't keep up with demand."

According to Sahai, the first lab swap diverted enough waste to fill a small swimming pool. "The numbers speak for themselves. It seemed like there was definitely a need," she said. Following the event, emails from researchers poured in, asking when the next event would be held.

"Hearing that type of response was empowering and made it feel like we really did make a single-day impact," Cisneros said.

The following year, the event partnered with the School of Engineering, had about 75 labs in attendance and saved researchers an estimated $60,000.

This year's event was hosted by the Stanford Bioscience Student Association and was co-sponsored by Peninsula Sanitary Service Inc. and the Stanford Property Management Office. At the end of the event, PSSI collected leftover materials and either disposed of the equipment properly or donated it to local high schools.

Spreading sustainability

In addition to diverting waste and saving money for researchers, a major aim of the lab swap event is to build an awareness of sustainability in labs.

"As older labs accumulate stuff, newer labs need some of these basic things to start out. This is a way of not tossing out perfectly good items," said Chelsea Longwell, a graduate student in chemical and system biology who took some freezer racks from the event.

According to Cisneros, an important goal of the lab swap is to build community around financial and environmental sustainability. This year's swap was just that — a sharing of not only materials, but of ideas, conversations and laughs at some of the outdated equipment.

"We can use sustainability to create community," Sahai said. "That's always fun to see." **ISM**

Mastectomy

continued from page 1

"Our findings suggest a limited understanding among physicians and patients of the meaning of genetic testing results," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "Clinical practice guidelines state that variants of uncertain significance should not be considered to confer high cancer risk, and that patients with these variants should be counseled similarly to a patient whose genetic test is normal. However, many of the physicians surveyed in our study stated that they manage these patients in the same way as they do patients with mutations known to increase a woman's risk."

> "We're learning that clinicians' knowledge of breast cancer genetics can be highly variable."

Only about half of the surveyed women who received genetic testing ever discussed their test results with a genetic counselor, and between one-quarter and one-half of the surveyed breast cancer surgeons indicated they treat women with VUS no differently than women with known cancer-associated mutations, the researchers found. Furthermore, some women undergo surgery prior to receiving genetic testing or seeing the results.

Kurian is the lead author of the study, which was published online April 12 in the *Journal of Clinical Oncology*. University of Michigan researchers Reshma Jagsi, MD, DPhil, and Steven Katz, MD, MPH, share senior authorship.

The need for genetic testing

The findings come on the heels of a February study by many of the same researchers showing that physicians often fail to recommend genetic testing for breast cancer patients at high risk for mutations in the BRCA1 or BRCA2 genes, which are strongly associated with ovarian and other cancers.

In this study, the researchers asked 2,502 women newly diagnosed with breast cancer whether they had received genetic testing, and if so, whether the testing and any discussion of results occurred before or after breast surgery.

They found that of the 666 women who had received testing, 59 percent were considered to have a high risk of a dangerous mutation in a cancer-associated gene. About one-quarter of these women had genetic testing only after surgery — meaning critical decisions were made about their care before information about their mutation status was available. Delays in testing were particularly pronounced in women who lacked private health insurance.

The researchers then polled the surgeons who treated the women in the survey. They found that, when compared with doctors who had treated 51 or more newly diagnosed breast cancer patients during the previous year, doctors who had treated fewer than 21 breast cancer patients were: less confident in discussing the results of genetic testing with patients, more likely to order the genetic test without referring women to a genetic counselor, less likely to delay surgery in order to have test results available for surgical decision-making and more likely to manage a patient with variants of uncertain significance in the same way they would manage patients with proven high-risk mutations in cancer-associated genes.

"Our findings suggest that we are not maximizing the benefit of genetic testing for our patients with breast cancer because of barriers related to timeliness of testing and lack of expertise necessary to incorporate results into treatment decisions," said Katz, who is a professor of medicine and of health management and policy at the University of Michigan.

Expertise to interpret the results

Although genetic testing has become more common and less costly, it's also become more confusing. The advent of multiplex gene panels that simultaneously test for mutations or variations in many different genes can render results that are difficult to interpret without the help of a trained genetic counselor. Uncertainties as to the meaning of test results may lead less-experienced surgeons to recommend aggressive treatment in the form of bilateral mastectomies, or cause women to opt for what they may feel is the safest option to manage their cancer.

Conversely, high-risk women who do carry dangerous mutations need this information to make informed decisions about their health care choices.

"The gaps identified in this study are striking," said Jagsi, professor and deputy chair of radiation oncology at the University of Michigan. "It is critical to ensure that patients at high risk for known cancer-associated mutations are fully informed of the potential benefits of genetic testing, and counseled accurately about the meaning of test results."

"We're learning that clinicians' knowledge of breast cancer genetics can be highly variable," said Kurian, who is a member of the Stanford Cancer Institute. "It's important for women at high risk of carrying a dangerous mutation to see someone with expertise in cancer genetics when planning their care. Unfortunately, in many cases genetic counselors may not be optimally integrated into the care of newly diagnosed cancer patients, making it difficult to rapidly triage these patients. Our study highlights the urgent need for improved patient access to cancer genetics experts, particularly genetic counselors, and for educating physicians about the appropriate use of genetic testing and interpretation of test results."

Researchers from the University of Southern California, Emory University and the Memorial Sloan-Kettering Cancer Center also contributed to the study.

The study was supported by the National Institutes of Health, the California Department of Public Health and the Centers for Disease Control and Prevention.

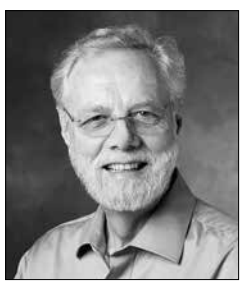
Kurian has received research funding from Invitae, Myriad Genetics, Ambry Genetics, GenDx and Genomic Health.

Stanford's departments of Medicine and of Health Research and Policy also supported the work. **ISM**

Sensor

continued from page 1

Conventional methods for diagnosing cystic fibrosis — a genetic disease that causes mucus to build up in the lungs, pancreas and other organs — require that patients visit a specialized center and sit still while electrodes stimulate sweat glands in their skin to provide sweat for the test. The electrodes can be annoying, especially for kids, in whom CF is most often diagnosed, Milla said. Then, children have to sit still for 30 minutes while an instrument attached to their skin collects sweat. Even then, the test isn't over, he said. Families wait while a lab measures the chloride ions in the sweat to determine if the child has cystic fibrosis.



Ronald Davis

Milla said this cumbersome method hasn't changed in 70 years. By comparison, the wearable sweat sensor stimulates the skin to produce minute amounts of sweat, quickly evaluates the contents and beams the data by way of a cellphone to a server that can analyze the results. The test happens all at once and in real time, Milla said, making it much easier for families to have kids evaluated.

Portable and self-contained

Additionally, people living in underserved communities or in out-of-the-way villages in developing countries, where conventional testing is unavailable, could benefit from a portable, self-contained sweat sensor, he said. The wearable device is robust and can be run with a smartphone, which can send measurements to a cloud and receive a result right back after review at a specialized center. CF diagnosis, as well as other kinds of diagnoses, could be done without needing a staff of skilled clinicians on duty and a well-equipped lab. "You can get a reading anywhere in the world," Milla said.

The sensor is not only for diagnosis and monitoring. It could also be used to help with drug development and drug personalization. CF is caused by any of hundreds of different mutations in the CF gene, so it's possible to use the sensor to determine which drugs work best for which mutations. "CF drugs work on only a fraction of patients," said Emaminejad, who is now an assistant professor of electrical engineering at UCLA. "Just imagine if you use the wearable sweat sensor with people in clinical drug investigations; we could get a much better insight into how their chloride ions go up and down in response to a drug."

For this study, the research team also measured glucose levels in sweat, which correspond to blood glucose levels, making the device potentially useful for monitoring pre-diabetes and diabetes. But the technology can also be used to measure other molecular constituents of sweat, such as sodium and potassium ions and lactate. The platform can be used to measure virtually anything found in sweat.

"Sweat is hugely amenable to wearable applications and a rich source of information," Davis said.

The team is now working on large-scale clinical studies to look for correlations between sweat-sensor readings and health. "In the longer term, we want to integrate it into a smartwatch format for broad population monitoring," Emaminejad said.

A wearable sweat sensor allows for frequent monitoring to see how patients respond to a treatment or if they're complying with treatment, Milla said. "It's a little like the old days when people with diabetes had to come into a clinic to get their glucose monitored. The real revolution came when people started to do their own finger stick, and nowadays you can even do it with continuous monitors."

Continuous monitoring

An important element of personalized medicine is establishing a baseline of normal values and variability for each individual. "When we were testing the device, we noticed that people had different sweat profiles. That showed we needed to calibrate accordingly," said Emaminejad. Once researchers have determined a personalized baseline through long-term monitoring, they can begin to spot changes in health status, he said.

Davis sees two major challenges with a wearable sweat sensor. One is reproducibility — that is, how consistent measures are in the same person from day to day or hour to hour. "Under the same biological conditions even with the same person, do you get the same number?"

> "Sweat is hugely amenable to wearable applications."

The second is mapping the molecular constituents of sweat. In short, what is in sweat that could reasonably be monitored to provide useful information about the body? "We're kind of limited with what we can actually measure so far. We can measure chloride, for example, so we're trying to figure out what we can use that for," Davis said.

He emphasized that the research is more than just the development of a device; it's a new way of understanding health — one which depends on continuous monitoring and a better understanding of individual health measures. It's an approach that could help prevent major illnesses in both individuals and populations.

Davis sees it as one way to head off pandemics. "For example, if I could sense that I'm coming down with a viral infection and my alarm goes off and says, 'You're coming down with a virus infection,' I should go home and not decide I'll push through it. It's not about me, it's about all of my colleagues." If everybody did that, he says, diseases wouldn't spread so quickly.

"If you could block a pandemic, it might even just die out," he added.

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-affiliated co-authors are research coordinators Zoe Davies, PhD, and Sean Ryan; graduate student Samyuktha Challa; and former Stanford research assistant Salmonn Talebi.

Davis is a member of Stanford Bio-X, the Stanford Cancer Institute and Stanford's Child Health Research Institute. Milla is also a member of the Child Health Research Institute.

Researchers at the UC-Berkeley also co-authored the paper.

The work was supported by the National Institutes of Health, the National Science Foundation, the Department of Energy and a Robert N. Noyce Fellowship in Microelectronics.

Stanford's departments of Electrical Engineering, of Biochemistry and of Genetics also supported the work. **ISM**

5 QUESTIONS

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

Christopher Almond on pediatric heart pump trial

During the wait for a heart transplant, patients with advanced heart failure can be supported with a ventricular assist device, an artificial pump that helps the heart move blood through the body. But the VAD now used for babies and small children — the Berlin Heart — has drawbacks. The pump carries a 30 percent risk of stroke and is unwieldy: The driver, which sits outside the body, is about the size of a shopping cart. For these reasons, children supported with the Berlin Heart must stay in the hospital until a donor heart becomes available. This can take months.

In recent years, researchers have developed a replacement for the Berlin Heart called the Jarvik 2015. The new device is a fully implantable pump that is roughly the length of a paper clip and as thick as an adult's index finger. After a series of successful animal studies, the Food and Drug Administration recently approved the first clinical trial of the device in humans. It's called the PumpKIN Trial after the NIH-sponsored Pumps for Kids, Infants and Neonates program that launched the research.

Christopher Almond, MD, an associate professor of pediatrics at the School of Medicine, is one of the trial's principal investigators. Erin Digitale recently asked him about the trial, which in May will begin enrolling children at Lucile Packard Children's Hospital Stanford and several other North American sites.

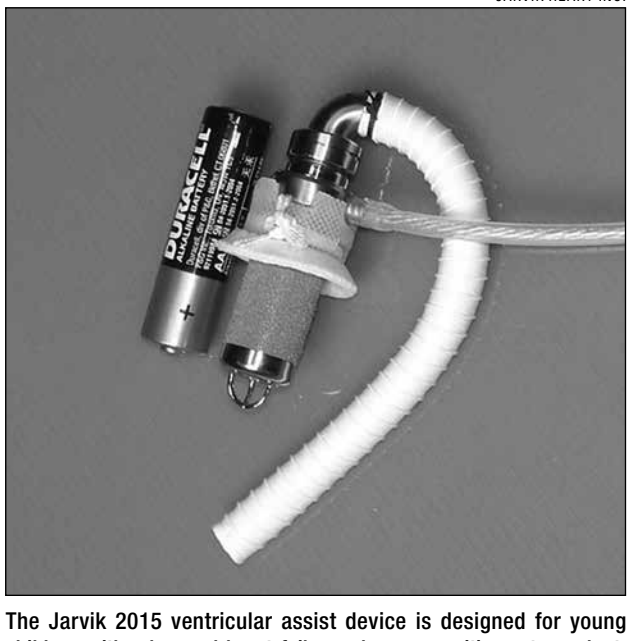
1 How does a ventricular assist device support the patient's health?

ALMOND: Infants and small children with severe heart failure have an unacceptably high risk of death on the transplant waitlist. A VAD helps to keep the child stable and capable of safely waiting out the time until a donor organ is available. Also, it's really miserable having heart failure — patients tend to have trouble breathing; have severe fatigue that keeps them bedridden; and have nausea, vomiting and loss of appetite that lead to malnutrition. In addition to improving survival, a VAD alleviates many of these symptoms by ensuring enough blood can get to the body's organs when the heart is weak. The goals of VAD support are to allow you to breathe comfortably, engage in exercise and tolerate excellent nutrition so that you become a better candidate for heart transplant. Beyond that, we ideally would like kids to go home with their VAD rather than being stuck in an ICU for weeks or months.

Christopher Almond

Having a heart pump can also give transplant doctors more time to find a heart that is the best match for the patient. Both of these factors lead to better outcomes after heart transplant.

JARVIK HEART INC.



The Jarvik 2015 ventricular assist device is designed for young children with advanced heart failure who are awaiting a transplant. Stanford will be one of the sites testing the device.

2 How does the Jarvik 2015 improve on the Berlin Heart?

ALMOND: There are several important limitations to the Berlin Heart, which is now the only heart pump approved by the Food and Drug Administration for infants and smaller children. First, the Berlin Heart has a high stroke risk — about 30 percent of all children supported across the United States have a stroke while on the device. Second, it lacks portability. Unlike adult VADs, which you can go home with, you cannot be discharged home with the Berlin Heart. Prolonged hospitalization carries its own risks and is often a significant social and financial hardship for patients and their families. Third, the Berlin Heart pump sits outside the body, connected to the child's heart through two large cannulas that pass through the skin. Cannula infections are another risk of the device.

By contrast, the Jarvik 2015 is a fully implantable device that uses continuous blood flow. This makes it similar to the latest generation of adult VADs, which have low stroke risk. So we hope that the Jarvik 2015 will have a lower stroke risk, and will eventually allow children to go home to wait for transplant. We also hope it will have a lower infection risk. In short, we want to close the technology gap between pediatric and adult VADs.

3 The new pump is named for Robert Jarvik, MD, who has spent his career designing different ventricular assist devices, as well as the first total artificial heart. What were some of the biggest challenges he and his team faced in developing this tiny pump?

ALMOND: The main challenge of miniaturizing any pump technology is to design it in a way that does not crush fragile red blood cells as they pass through the device, which is spinning several thousand times per minute. An earlier version of the Jarvik 2015 pump tended to break red blood cells and had to be redesigned. Interestingly, a relatively minor design change caused a big reduction in the pump's red cell breakage.

A second challenge is that the flow rate through miniature pumps is much slower than for adult pumps, greatly increasing the chance that clots can form inside the pump. When clots form, they can break off and travel through the bloodstream to the brain, causing a stroke. For example, blood typically flows through an adult heart pump at 1.5 to 2 gallons per minute, making it less likely to slow down and clot. Blood flows through an infant pump at about one-eighth to one-quarter of a gallon per minute, making it more likely to clot. However, the Jarvik 2015 pump has a relatively low risk of clot formation.

4 How will the trial work?

ALMOND: This multicenter, randomized clinical trial will enroll 88 patients at 22 pediatric heart transplant centers in North America. Stanford is providing leadership for the trial, which will enroll children with advanced heart failure who weigh between 18 and 44 pounds and need a heart transplant. They will be randomly assigned to receive a Berlin Heart or a Jarvik 2015, with half of the patients in each group. For the trial, all study participants will need to stay in the hospital so we can carefully evaluate the safety of the new pump. But if the pump proves to be safe enough, the longer-term goal is to discharge patients home with the device to wait for their heart transplant.

5 How does Stanford's leadership role in this trial fit in with our larger history as a center of innovation in heart transplant?

ALMOND: Stanford has been a pioneer in developing cardiac transplantation and therapies for children with end-stage heart failure. In 1984, we performed one of the world's first heart transplants in a young child. We have been refining pediatric heart-transplant techniques ever since.

Stanford has also been a pioneer in the field of heart pumps. In 2004, Packard Children's was one of the very first U.S. hospitals to use the Berlin Heart. Until that time, the Berlin Heart had been used primarily in Europe. Under the direction of pediatrician David Rosenthal, Packard Children's petitioned the FDA to import the device from Germany for a 5-month-old boy, who was then the youngest child in the world to receive the pump. This little boy did well and got a heart transplant after 55 days. The novel use of the Berlin Heart in this child ended up on the front page of *The New York Times* and served to catalyze interest in the device across the United States. Stanford faculty provided important leadership for the multisite clinical trial of the Berlin Heart, which led to its FDA approval in 2011. Stanford physicians have been on the forefront of the use of VADs in children with single-ventricle heart disease and in children with muscular dystrophy or other contraindications to heart transplant. Today, Stanford Children's Health has one of the busiest pediatric VAD programs in the country. **ISM**

Blood

continued from page 1

feet high, that is brightly lit and open to the surrounding environment — two factors that make mice feel insecure. The table is also full of holes, one of which is attached to a tube in which a scared mouse can find darkness and safety. The other holes offer only a drop to the floor from a height that would not physically harm a mouse but is enough deter one. Which hole has a burrowing tube attached to it can be changed from one session to the next. Visual cues to its location can also be transferred to help guide the mouse to the escape hole, memory permitting.

Improvements in function

When the older mice received human umbilical-cord blood plasma every fourth day for two weeks, many measures of hippocampal function improved notably. Plasma from older people, on the other hand, didn't help at all, while young-adult plasma induced an intermediate effect. And older mice's performance on the Barnes maze and other tests was stellar in comparison with mice of the same age who got injections of saline instead of plasma.

Something in umbilical cord blood was making old brains act younger. To find out what it was, Wyss-Coray and his colleagues gauged plasma-protein levels in humans and mice from different age groups, in search of proteins that the two species share in common and whose levels change similarly with age. One protein in particular grabbed their attention: In a laboratory test designed to discern a substance's ability to enhance nerve-cell activity in the brain, it triggered this activity to a great degree. The protein, called tissue inhibitor of metalloproteases 2, or TIMP2, belongs to a well-known family of four TIMPs that regulate the activity of other proteins whose function is to chop up yet other proteins occupying the matrix in which cells are embedded.

Injecting TIMP2 by itself into elderly mice largely duplicated the beneficial effects of umbilical-cord plasma. It even restored these mice's nesting capacity: an instinctive penchant, largely lost in old age, for using available materials, such as cotton wads supplied by the researchers, to build nests in which mice typically prefer to sleep. But old mice that were given human cord plasma depleted of TIMP2 derived no learning and memory benefits. And administering TIMP2-neutralizing antibodies to young normal mice, who ordinarily perform well on memory tests, obliterated their prowess.

Joseph Castellano

"TIMP2's effects in the brain have been studied a little, but not much and not in aging," said Castellano. "In our study, it mimicked the memory and learning effects we were getting with cord plasma. And it appeared to do that by improving hippocampal function."

Stanford's Office of Technology Licensing has filed for patents related to the findings in the study. Alkahest, a biotechnology company based in San Carlos, California, in which Castellano and Wyss-Coray hold equity and which Wyss-Coray co-founded, has licensed rights to this intellectual property.

Other Stanford co-authors of the study are former graduate student Kira Mosher, PhD; former research assistant Rachelle Abbey; research technician Alisha McBride; research scientist Daniela Berdnik, PhD; research associate Jadon Shen; research nurse manager Martha Tingle, RN; former mass-spectroscopy specialist Izumi Hinkson, PhD; Xinmin Xie, MD, PhD, a consulting associate professor of anesthesiology, perioperative and pain medicine; Michelle James, PhD, assistant professor of radiology and of neurology and neurological sciences; and Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine.

The study was funded by the National Institute on Aging, the Jane Coffin Childs Foundation, the Simons Foundation, the U.S. Department of Veterans Affairs, the Glenn Foundation for Medical Research and the Stanford Brain Rejuvenation Project.

Stanford's Department of Neurology and Neurological Sciences also supported the work. **ISM**

Surgeon-scientist, advocate for diversity in medicine to speak at diploma ceremony

Augustus White III, MD, PhD, the first African-American to graduate from the Stanford School of Medicine, will be this year's speaker at the school's diploma ceremony.

The ceremony will be held from 1-3 p.m. June 17 on Alumni Green, next to the Li Ka Shing Center for Learning and Knowledge. No tickets are required.

Throughout his career as an orthopedic surgeon and scientist, White has remained a pioneer and role model for underrepresented minorities in the medical profession. His early interest in orthopedics stemmed from his athletic career as an undergraduate at Brown University, where he played football. At Stanford, where he served as president of the medical student body, he became interested in spinal motion and back pain. He earned a medical degree from Stanford in 1961 and his PhD from the University of Gothenburg at the Karolinska Institute for research on the analysis of spinal motion in 1969.

Augustus White III

White is an internationally known, widely published authority on biomechanics of the spine, fracture healing and surgical and nonsurgical care of the spine. He has authored or co-authored more than 200 scientific and clinical publications, including chapters, books and articles — among them the book *The Clinical Biomechanics of the Spine*.

White served as orthopedic surgeon-in-chief at Harvard Medical School for 13 years.

Since his retirement from the operating room in 2001, White has focused on how prejudice can get in the way of good medicine, and in 2011, he wrote the memoir, *Seeing Patients: Unconscious Bias in Health Care*.

He is the Ellen and Melvin Gordon Distinguished Professor of Medical Education at Harvard Medical School. **ISM**

Stanford collaboration with pharmaceutical company funds two new projects

Two research projects have been selected for one-year funding by the Stanford Center for Clinical Research and the pharmaceutical company AstraZeneca.

This is the second year of a three-year collaboration between the organizations. The focus of the collaboration is cardio-metabolic and respiratory diseases, oncology, mobile health, innovations in clinical trial design and operations, and education and training initiatives.

The 2017-18 grantees and their projects are:

• Daniel Rubin, MD, MS, associate professor of biomedical data science, of radiology and of medicine, who is using electronic health records from multiple institutions to build statistical models that will relate patient treatments to outcomes. Focusing on metastatic breast cancer, he will compute predictive statistical models to identify best treatments, such as the decision about when to switch from endocrine therapy to chemotherapy, which chemotherapy drug to administer and when to stop one treatment or start another. Ultimately, he hopes to expand this infrastructure to develop decision models for a variety of diseases.

• Tina Hernandez-Boussard, PhD, associate professor of medicine, of surgery and of biomedical data science, who proposes building a tool that will automate the manual and extremely labor-intensive staging of prostate cancer using both clinical and pathological data captured in the electric health record. She hopes such automated staging will improve care coordination, physician workload, hospital certification and national cancer surveillance efforts.

The Stanford-Astra-Zeneca collaboration is distributing $2 million over three years to support six innovative research projects by Stanford investigators. The projects each receive $260,000. **ISM**

Trial led by Mark Genovese wins Clinical Research Forum award

By Bruce Goldman

A clinical trial led by Mark Genovese, MD, Stanford professor of immunology and rheumatology, has been recognized by the Clinical Research Forum as one of the top 10 clinical studies of 2016.

The studies reflect major work being conducted at nearly 60 research institutions and hospitals across the United States, as well as at partner institutions from around the world.

Mark Genovese

Known as the RA-BEACON trial, the multicenter study headed by Genovese, who holds the James W. Raitt, MD, Professorship, tested a new rheumatoid arthritis drug, baricitinib, in more than 500 patients for whom other therapies had failed. The new drug was found to be safe and effective, significantly improving the conditions of more than 50 percent of the patients within 12 weeks. The improvements seen in all groups of patients treated with baricitinib largely remained at 24 weeks.

The Clinical Research Forum is dedicated to providing leadership to the clinical and translational research enterprise and to promoting understanding and support for clinical research and its impact on health and health care.

The organization conducts annual competitions to determine the 10 outstanding research accomplishments in the United States. Winners are chosen based on the degree of innovation and novelty involved in the advancement of science; contribution to the understanding of human disease or physiology, or both; and potential impact upon the diagnosis, prevention and/or treatment of disease.

The awards were presented April 18 at a ceremony at the National Press Club in Washington, D.C. Members of the RA-BEACON research team visited congressional representatives on Capitol Hill on April 19 to brief them on findings of the trial and the critical and necessary role of federal funding for clinical research. **ISM**

OF NOTE

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

AMIN AALIPOUR, an MD-PhD student, was named a 2017 Paul & Daisy Soros Fellow. The fellowship of up to $90,000 is given to 30 immigrants or children of immigrants who are poised to make significant contributions to the nation through their work. A graduate of Stanford with bachelor's and master's degrees from the School of Engineering, Aalipour is working in the lab of professor and chair of radiology Sanjiv "Sam" Gambhir, MD, PhD, to develop early-cancer-detection technologies and immunotherapies.

Amin Aalipour

MARIA FILSINGER INTERRANTE, an MD-PhD student, is part of a team of Stanford students that has won the "Cure it!" Lemelson-MIT Student Prize, which honors promising collegiate inventors in the United States. Her three-member team will share the $10,000 cash prize. The team engineered proteins that could help combat multi-drug-resistant bacteria.

Maria Filsinger Interrante

TERI KLEIN, PhD, was appointed professor (research) of biomedical data science and of medicine, effective March 1. Her research interests include pharmacogenetics, precision medicine, computational biology and bioinformatics.

Teri Klein

WILLIAM NEWSOME, PhD, the Harman Family Provostial Professor, the Vincent V.C. Woo Director of the Stanford Neurosciences Institute and professor of neurobiology, was elected to the American Academy of Arts and Sciences. Founded in 1780, the academy brings together leaders from the academic, business and governmental sectors to respond to challenges facing the nation and the world. Newsome is one of 228 new members, including 10 other Stanford faculty members, who will be inducted in October in Massachusetts. His research examines the neuronal processes that mediate visual perception and visually guided behavior.

William Newsome

PAUL NUYUJUKIAN, MD, PhD, was appointed assistant professor of bioengineering and of neurosurgery, effective April 1, 2017. He directs the Brain Interfacing Laboratory. His research focuses on the use of brain-machine interfaces to study and treat a variety of brain-related medical conditions such as stroke and epilepsy.

Paul Nuyujukian

KT PARK, MD, was promoted to associate professor of pediatrics, effective March 1. He is the co-director of the Stanford Children's Inflammatory Bowel Disease Center. His research uses big data, patient-reported outcomes and decision science to improve the efficacy and cost-effectiveness of diagnostic tools and therapies for gastrointestinal diseases.

KT Park

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, was awarded a 2017 NARSAD Independent Investigator Grant in schizophrenia from the Brain & Behavior Research Foundation. The grants, which provide $50,000 a year for up to two years, are given to 40 mid-career scientists to fund basic research, new technologies, diagnostic tools and therapies for mental illness. Pasca will use a human 3-D brain-culture system developed in his lab to study glial and neural abnormalities in patients with 22q11.2 deletion syndrome, a genetic condition that confers a high risk of schizophrenia. **ISM**

Sergiu Pasca

Andrew Hoffman, Ann Weinacker appointed senior vice chairs in Department of Medicine

Professors of medicine Andrew Hoffman, MD, and Ann Weinacker, MD, have been named senior vice chairs in the Department of Medicine.

The appointments are part of an effort to strengthen relationships between the Department of Medicine and other organizations and departments within Stanford Medicine, according to Robert Harrington, MD, chair of the department and the Arthur L. Bloomfield Professor of Medicine.

Andrew Hoffman

Ann Weinacker

Hoffman, an endocrinologist, will serve as senior vice chair for academic affairs. He will work to bridge the department's research and education endeavors and others under way at the School of Medicine.

Weinacker, a pulmonologist and critical-care specialist who serves as the associate chief medical officer of patient care services at Stanford Health Care, has been named senior vice chair for clinical operations. She will represent the department on clinical issues and collaborate with Stanford Health Care. **ISM**