

A center has been established to help researchers probe the structure of biological molecules.
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David Entwistle named Stanford Health Care president and CEO

Stanford Health Care announced April 13 that its board of directors has appointed David Entwistle as president and CEO, effective July 5.



David Entwistle

Currently chief executive officer at University of Utah Hospitals & Clinics, Entwistle will succeed Mariann Byerwalter, who has served as interim president and CEO since January.

“David Entwistle has a distinguished record of accomplishment and dedication to the critically important role of academic medical centers in advancing human health,” said SHC board Chair John Levin. “As we plan for the opening of the new Stanford Hospital in 2018 and continue to innovate across the entire continuum of care, his commitment to combining the highest levels of quality with outstanding patient experience will help achieve SHC’s inspiring vision for the future.”

For 2015-16, *U.S. News & World Report* ranked SHC’s Stanford Hospital as the No. 1 hospital in California, with top-tier rankings in 13 of 16 specialties, as well as recognition on the national top 15 “Honor Roll.”

Entwistle has led University of Utah Hospitals & Health Systems since 2007. As the only academic medical center in a region that includes Utah and five surrounding states, UUHC has 1,100 board-certified physicians who staff four university hospitals, 10 community clinics and several specialty centers. It is consistently ranked among *U.S. News & World Report*’s “Best Hospitals” and in 2010, was No. 1 on the prestigious University HealthSystem Consortium’s Quality and Accountability scorecard, achieving top 10 status in subsequent years.

“We are on the brink of an amazing transformation in how we approach health,” said Stanford School of Medicine Dean Lloyd Minor, MD. “David Entwistle is a proven leader who will collaborate effectively with Stanford Medicine physicians and with all our partners as we pursue the tremendous potential

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Newly discovered immune cell linked to inflammatory disease

NORBERT VON DER GROEBEN



Cornelia Weyand and her colleagues found that certain regulatory T cells become less effective at fighting inflammation as we grow old.

By Bruce Goldman

School of Medicine researchers have unraveled the workings of an important type of immune cell whose existence was unknown just a few years ago.

The scientists found that this cell type keeps a lid on immune response, preventing runaway inflammation. But it becomes rare and malfunction-prone in even healthy people’s bodies as they get older. That could help to explain why our immune systems go increasingly haywire with advancing age.

The researchers identified the primary cause of these cells’ malfunction and linked it to an auto-inflammatory disorder, giant cell arteritis. They suspect this connection may hold for some far more common age-related conditions, too.

The findings, described in a study published April 18 in the *Journal of Clinical Investigation*, suggest possible new approaches to restoring function in these cells.

Just as the immune system’s assault brigades must expand and become warlike when confronting a pathogen or incipient tumor, they must contract and become peaceful afterward, lest they harm healthy tissues, said the study’s senior author, Cornelia Weyand, MD, professor and chair of immunology and rheumatology. First authorship is shared by postdoctoral scholar Zhenke Wen, MD, PhD, and visiting scholar Yasuhiro Shimojima, MD, PhD.

‘Built-in brakes’

“Fortunately, the immune system has built-in brakes,” said Weyand. “We call them regulatory T cells, or Tregs.”

When a pathogen invades the body or a cancerous cell emerges or a vaccine dose is administered, the immune system ramps up, producing antibodies and attacking suspected infected or

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Study: Low-risk drinking guidelines vary widely among countries

By Krista Conger

People monitoring their alcohol intake often rely on governmental guide-

lines to assess whether how much they’re drinking is likely to have adverse health effects.

But researchers at the School of Medi-

cine have found that such guidelines for low-risk drinking vary widely among countries. Some, like the United States, assign different daily or weekly limits for men and women, while others, like Australia, don’t differentiate by gender.

Furthermore, the amount of alcohol in each country’s “standard drink” can range from 8 to 20 grams. Toss in the need to calculate — on the fly — how many grams each drink contains based on the volume, which could be listed in ounces, milliliters or even imperial pints, and the alcohol content of the type of beverage in question (is it indicated as a percentage? a proof? as “alcohol by volume”?) and you’ve got a major headache even before you’ve taken that first sip.

It’s confusing, to say the least —

both for people trying to drink responsibly and for researchers wishing to study global patterns of alcohol use and addiction.

“There’s a substantial chance for misunderstanding,” said Keith Humphreys, PhD, a professor of psychiatry and behavioral sciences at Stanford. “A study of the health effects of low-risk drinking in France could be misinterpreted by researchers in the United States who may use a different definition of drinking levels. Inconsistent guidelines are also likely to increase skepticism among the public about their accuracy. It is not possible that every country is correct; maybe they are all wrong.”

A paper describing the researchers’ findings were published online April 12

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ALEXEY LYSENKO / SHUTTERSTOCK.COM

Stanford, Intermountain physicians discuss joint projects

By Ruthann Richter

For many medical problems, there is more than one solution and often wide variations among physicians as to which tool or treatment they use. For instance, for a child with enlarged tonsils, a surgeon may choose among many different surgical instruments to effectively remove them. But is one method better than the others, both in terms of the child's welfare and overall health-care costs?

For the last few decades, Intermountain Healthcare, a not-for-profit health-care system based in Utah, has made an art of dissecting these issues by analyzing data to develop standards of care that reflect what works best for patients and is most affordable. Now physicians at Stanford Medicine are hoping to learn from that experience.

"Intermountain has become a world leader in terms of managing clinical care in a way that reduces the variability of care and improves quality while reducing costs," said Bryan Bohman, MD, clinical associate professor of anesthesia at the School of Medicine and associate chief medical officer at Stanford Health Care. "They're thought of as one of the very top organizations in learning to manage clinical care. That's one reason we are partnering with them."

On April 14, Bohman was among 17 Stanford Medicine clinicians and administrators — including Lloyd Minor, MD, dean of the Stanford School of Medicine, who led the group — who went to Utah to hear from Intermountain specialists how they have used evidence from large, published studies and detailed data from their approximately 850,000 patients to improve care while saving money both for patients and insurers.

New collaboration

The visit was part of a major new collaboration between the two institutions, which will spend \$3.75 million to enable joint clinical, research and education projects that are expected to benefit both — and possibly the U.S. health-care system at large. Intermountain is contributing \$2.5 million to the partnership, while Stanford will provide \$1.25 million.

"Stanford Medicine is honored to be collaborating with such an innovative and integrated health delivery system," Mi-

nor said. "Our partnership will result in higher quality care for both Stanford and Intermountain patients while establishing models that can be adopted by health-care organizations around the world."

The partnership will span a range of projects in cancer, heart disease, pediatrics and other specialties, as well as improvements in clinical care and an exchange of trainees who will do rotations at the two institutions.

"There is such great potential to work together," Charles Sorenson, MD, president and CEO of Intermountain, said during the April 14 meeting. "Investment in these collaborative projects will be beneficial to you at Stanford, as well as us."

'A really good fit'

About two years ago, Sorenson said, Intermountain began looking for a "nationally recognized, admired partner" in academia. Intermountain already had a connection to Stanford through Arnold Milstein, MD, a professor of medicine and director of Stanford's Clinical Excellence Research Center, who used the health-care system as a pilot site for his "ambulatory care ICU" project, a new form of outpatient care to prevent costly and dangerous health crises in patients with chronic disease. Milstein is now on the board of Intermountain.

Other physicians, including Bohman, have attended Intermountain's Advanced Training Program, led by Brent James, MD, executive director of the Intermountain Institute for Health Care Delivery Research and the guru of standardized clinical care.

After a preliminary meeting between leaders at Stanford and Intermountain, "it became obvious there was a really good fit in terms of mutual benefit," Bohman said. "They wanted an academic partner with a deep reserve of outstanding scientists, including innovative analytics and informatics. We were looking to their very large clinical population that would help us in terms of clinical trials, in the training of house officers and in doing collaborative research."

Among the joint research projects in the offing is a cancer genomics study. The institutions will form a consortium to share molecular tumor data on a range of

tumor types including breast, colon and esophageal tumors. Genetic data will be linked with outcomes data from targeted therapies with an eye to developing better treatments, said Eben Rosenthal, MD, a professor of otolaryngology and medical director of the Stanford Cancer Center.

"When you do genetic testing on a tumor, there are dozens of mutations of unknown certainty," Rosenthal said. "Are they driving the tumor or are they incidental? Can they be targeted with a drug? And what is the outcome of a drug?"

"If we can pool our data, we can learn a lot more about these relatively rare mutations," he added. "The power of that, from the standpoint of Intermountain, is that we have really smart people to do the data analysis and cutting-edge science, while they have a huge population for which they have rigorously maintained records. To me, that just has massive potential to make an impact."

Intermountain has the nation's largest biorepository, started in 1975, which stores more than 3 million tissue samples used for the advancement of cancer treatment and other research. Stanford oncologist James Ford, MD, associate professor of medicine, is leading the project in collaboration with Lincoln Nadauld, MD, PhD, at Intermountain.

Antibiotics in newborns

In another project, Jochen Profit, MD, assistant professor of pediatrics, is working with Intermountain neonatologists on an issue of national concern in the field: the overuse of antibiotics in newborns.

A recent, landmark study by the California Perinatal Quality Care collaborative, housed at Lucile Packard Children's Hospital Stanford, showed wide variations in use of antibiotics among sick newborns in intensive care units. That has led to a major effort among California NICUs, including Packard's, to reduce use of these drugs, particularly for sepsis, Profit said.

Sepsis is a rare infection, but it can be life-threatening and there is no easy way to detect who is at risk for the disease, he said. So the tendency is for doctors to overtreat with antibiotics, which can lead to serious complications.

Profit is working with neonatal inten-

sive care units across the state to integrate an Intermountain training program to minimize unnecessary antibiotic use and generally improve quality of care for these infants.

"They [Intermountain] have this culture of quality, where they constantly think about how to improve, even in many areas where they are already national leaders," Profit said. "It's a different attitude than you see at a lot of hospitals."

Care pathways

Stanford Medicine physicians also hope to benefit from adopting some of the "care pathway" models for which Intermountain is well-known. These are care guidelines that specify use of certain drugs and treatments for a given condition, based on scientific evidence. These guidelines help reduce variations in practice among physicians and improve patient outcomes.

As Intermountain cardiologist Donald Lappé, MD, said, "We're reducing variability of care because you can't manage chaos. You can't improve quality if you can't manage the care process."

Cardiologist Paul Heidenreich, MD, professor of medicine and of health research and policy at Stanford, said Stanford Health Care plans to adopt an Intermountain care pathway for patients who come into the emergency room in the throes of a heart attack. Among other things, these patients will receive one of a few specific antiplatelet medications, which help treat and prevent blood clots that are often the cause of the heart attack. Standardizing drug choices helps reduce errors and improve patient safety because trainees, nurses and other clinicians can use standard order sets and don't have to wait to determine the preferences of attending physicians, which can vary widely, Heidenreich said.

This approach also enables physicians to focus on what may be uniquely different about the patient, Bohman said. "Care pathways align the entire health-care team to ensure that the basic blocking and tackling are reliably performed, allowing the physician to focus on humanistic aspects of care as well as any unusual aspects that may actually require a different treatment," he said. **ISM**

Stanford Medicine to join new Parker Institute for Cancer Immunotherapy

By Becky Bach

A center is being created at Stanford Medicine as part of the new Parker Institute for Cancer Immunotherapy, a multi-institution effort established with a \$250 million grant from the Parker Foundation.

Crystal Mackall, MD, professor of pediatrics and of medicine, will lead the Stanford center, which is being launched

with an initial \$10 million grant from the foundation, with additional support expected in the following years. The foundation was established by Silicon Valley entrepreneur and philanthropist Sean Parker, who co-founded the Internet file-sharing service Napster and served as the first president of Facebook.

"This unprecedented institute captures the essence of our vision for precision health, which is allowing us to use

immunotherapy and other approaches to prevent diseases like cancer before they strike — and cure them decisively if they do," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "We are thrilled to partner in this initiative with the Parker Foundation and our peers, working together with them to bring about a better future for cancer patients everywhere."

The new institute includes six university-based centers, as well as partnerships with biotechnology and pharmaceutical companies and with nonprofit health organizations.

Although advances in radiation and drug treatment of cancer have helped many patients, cancer immunotherapy — the use of the body's immune system to attack cancer cells — has the promise to dramatically change cancer outcomes, the institute's founders say. The creation of the institute is timely because the cancer immunotherapy field is at an "inflection point," Parker has said. That message was echoed by Mackall.

"The Parker-Stanford partnership will

create a powerful synergy that will enable the deep scientific and clinical resources within Stanford Medicine to be rapidly and efficiently translated into new immunotherapies for patients with cancer," Mackall said.

The Stanford center will include a core team of researchers, including Mark Davis, PhD, professor of microbiology and immunology and director of the Stanford Institute for Immunity, Transplantation and Infection.

"It's exciting to be joining this unique effort to pool the efforts of six different medical centers to focus on advancing cancer immunotherapy," said Davis, who is also the Burt and Marion Avery Family Professor. "It's also a testament to the expertise we have built up here at Stanford over the past 10 years to develop new methods to analyze the immune responses of patients with cancer and other diseases."

Mackall is also associate director of the Stanford Cancer Institute and co-medical director of the Stanford Laboratory for Cell and **See PARKER, page 3**



Sean Parker

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Family travels coast to coast for child's lifesaving heart surgery

By Tara Stultz

To the casual observer, Alexander Bracebridge is just another curious, fun-loving 22-month-old. He enjoys running, throwing balls, taking swimming lessons and playing with TV remotes. When he wants to go outside, he lets his parents know by bringing his shoes to them.

First-time parents Russ and Robyn Bracebridge don't take these seemingly ordinary moments for granted. That's because their son was born with a rare heart condition called tetralogy of Fallot, which consists of several related defects present at birth.

This past fall, the Bracebridges traveled nearly 3,000 miles from their home in northern Virginia to Lucile Packard Children's Hospital Stanford so that Frank Hanley, MD, could perform a complex, 12-hour surgery on Alex. Hanley, a professor of cardiothoracic surgery at Stanford and chief of pediatric cardiac surgery at the hospital's Children's Heart Center, has helped Alex and thousands of other children with serious heart conditions lead normal lives.

Hanley invented and perfected an innovative surgical technique called unifocalization to treat ToF. His remarkable 98 percent success rate with the procedure, which allows him to do in one marathon surgery what other surgeons would stage over months or years, has helped him build the largest program anywhere for this complex surgery. It's a program noted by the Children's Hospital Association for having exceptional outcomes — even while tackling the most complex cases in the country.

An extreme form of ToF

"We are grateful that the surgeon who pioneered unifocalization was willing to do the surgery for Alex, and we're even more grateful that the outcome was so good," Russ said.

The Bracebridges are just one of countless families that have traveled from around the corner and around the world so that Hanley could perform their child's surgery. From Germany to South Africa to the Bay Area, Hanley has built a "destination program," with the most challenging types of pediatric heart surgeries performed routinely — even those that many other centers can't or won't attempt.

ToF occurs in about 1 of every 1,000 babies because of abnormal development of the fetal heart during the first eight weeks of pregnancy. In infants like Alex with the most complex form of this condition, the blood vessels that should connect the heart to the lungs instead connect the lungs to the aorta, the body's main



Robyn and Russ Bracebridge with their son, Alexander, who was treated for a rare heart condition at Lucile Packard Children's Hospital Stanford.

artery, and the heart has a hole in the wall separating its lower chambers, or ventricles.

"This extreme form of ToF occurs in about one-fifth of cases," Hanley said. Complex ToF also includes pulmonary atresia — a missing heart valve between the pumping chamber of the heart and the lungs — and major aortopulmonary collateral arteries — small arteries that develop to supply blood to the lungs to compensate when pulmonary circulation is underdeveloped.

This abnormal anatomy increases lung blood pressure, which can damage the lungs and prevent the body from receiving fully oxygenated blood. Hanley's one-stage unifocalization for complex ToF corrects this problem by combining the collateral arteries into one unified, functioning pulmonary artery.

Reoperative cases take experience, skill

Alex had his first major ToF surgery at an East Coast center in late 2014 when he was 5 months old. While the procedure initially addressed some issues, follow-up tests during the next 10 months showed that Alex's right pulmonary branch remained small, and he faced

other serious problems.

The Bracebridges, who learned of Hanley and his pioneering surgical techniques from Alex's cardiologist, thought he might be able to help. They were right.

Last October, shortly before Alex turned 16 months, Hanley performed a unifocalization to address the lingering pulmonary artery problem. He likens a pulmonary artery to an oak tree with a trunk, branches and then more branches — with the potential for blockages anywhere along the way. "Alex had blockages way out on the secondary and tertiary areas affecting both of his lungs, which we were able to correct," he said.

Alex also had a dangerous bulge on his pulmonary artery called a "pseudoaneurysm," caused by high lung blood pressure, which Hanley successfully removed. "They can get larger and larger and cause fatal complications," he explained. He also replaced the first donor heart valve that Alex received and closed a small hole in his heart.

The surgery was 12 grueling hours, with no breaks for Hanley and his team. Alex showed dramatic improvements in his pulmonary blood pressure and blood flow almost immediately. It was, Robyn said, "the best news we could have hoped for."

While unifocalization is ideally performed by Hanley during the first few months of an infant's life, about 30 percent of his ToF cases are reoperations like Alex's, in which an initial surgery was performed elsewhere but serious problems remain.

"Unifocalization is more complex when these children have already had surgery, so it's best if we have the first shot for the best outcomes. However, Alex's result with the reoperation was very, very good," Hanley said.

So good, in fact, that Alex has already successfully met several post-surgical milestones. If everything is progressing as hoped at Alex's one-year cardiology visit, he will only need routine checkups once or twice a year.

Alex will periodically outgrow his heart valves "just like kids outgrow shoes," Hanley explained — but the operations to replace them are simple compared with the unifocalization. And once Alex is fully grown, a replacement valve will be needed every decade or two.

Hanley's pioneering approach is another chapter in the story of Stanford Medicine's ongoing innovation in cardiac care. In 1968, Stanford's Norman Shumway, MD, pioneered America's first successful human heart transplant. It's where the first pediatric heart-lung transplant in the country was performed. And today, Stanford is home to 20 clinical trials in pediatric cardiovascular medicine, while scientists at the Stanford Cardiovascular Institute are researching the origins of congenital heart disease and pediatric heart failure.

Spreading the word

Throughout their journey, the Bracebridges have received encouragement from other parents through online and in-person congenital heart defect support groups. When Alex's cardiologist recommended Hanley, they were able to quickly connect with parents whose children had successfully undergone surgery with him.

"Dr. Hanley's name should be on the tip of everyone's tongue when a baby is diagnosed with a complex heart problem," Robyn said.

Now, the Bracebridges pay it forward every chance they get: Robyn even serves as a co-leader of the Washington, D.C., chapter of Mended Little Hearts, a non-profit that supports children with congenital heart defects and their families.

A bright future

Looking ahead, the Bracebridges' experience has given them some added perspective when it comes to the hopes and dreams that all parents have for their children.

"I want him to do whatever he wants, to do sports if he wants, or be a 'nerd' — whatever he wants to be, as long as he's happy," Russ said.

Russ and Robyn's greatest hope is for Alex to live a long, healthy, high-quality life, which they now believe is possible.

"Because of Dr. Hanley," Robyn said, "Alex's future is so much brighter." ISM

Parker

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Gene Medicine. She specializes in T cell homeostasis, the maintenance of a healthy number and diversity of these cells. She previously led the Immunology Section at the National Cancer Institute.

The other five participating centers are Memorial Sloan Kettering Cancer Center; the University of California, Los Angeles; the University of California, San Francisco; the University of Pennsylvania; and the University of Texas MD Anderson Cancer Center.

The Parker Foundation established the Sean N. Parker Center for Allergy & Asthma Research at Stanford in 2014 with a \$24 million gift. ISM

NORBERT VON DER GROEBEN



Crystall Mackall will lead the Stanford Medicine center that is part a multi-institution effort to advance cancer immunotherapy.

Symposium on teaching bedside medicine set for Aug. 27-28

Registration is open for the Stanford 25 Skills Symposium 2016.

The two-day event, scheduled for Aug. 27-28, is designed for early and mid-career physicians who teach clinical skills. It will take place at the Li Ka Shing Center for Learning and Knowledge.

The interactive program aims to help participants become more effective at teaching bedside medicine and provides a community of like-minded practitioners.

Mornings will be spent in plenary sessions and afternoons will have five tracks from which to choose: bedside ultrasound, Stanford Medicine 25, outpatient, 5-minute bedside moment and clinical skills assessment.

To learn more about the symposium and register, visit <http://stanfordmedicine25.stanford.edu/about/symposium.html>.

Attendance is limited to ensure that adequate opportunities for learning and practicing are available for each participant. ISM

Your one-stop shop for producing and crystallizing biomolecules

By Amy Adams

A new center has been established on campus to help researchers probe the structure of biological molecules.

Housed in the basement of the Shriram Center, the Macromolecular Structure Knowledge Center contains equipment and resources for producing and crystallizing biological molecules. Among the incubators full of cells churning out molecules and crystals slowly growing in stacks of lab dishes, you'll also find Marc Deller, DPhil, who heads MSKC. He serves as a bridge between Stanford scientists hoping to understand molecular structures and the SLAC National Accelerator Laboratory, which has the SSRL Synchrotron and LCLS X-ray laser for carrying out X-ray crystallography and other structural biology techniques.

Stanford scientists can already use SLAC facilities, and many discoveries in basic structural biology and in developing drugs have been the result. But what many Stanford researchers don't have is the equipment for testing hundreds of different crystallization conditions or expertise in working with challenging molecules.

Deller has both. He has spent the past 15 years in academia and industry carrying out high-throughput protein expression, purification and crystallization, and determining molecular structures.

Crystallization resource

"It takes a bit of knowledge to know which crystallization screens to use because some are designed for a particular kind of protein, or to know how to improve the quality of the crystals for optimal data collection at SLAC," Deller said.

One researcher who has already found

the center useful is postdoctoral scholar Lindsay Deis, PhD. She had prior experience in structural biology when she joined the lab of Peter Kim, PhD, professor of biochemistry, but Kim's lab didn't have some of the equipment Deis needed for higher-throughput crystallography.

"The MSKC opened up all these possibilities for doing structural biology," she said. "We probably could have made progress, but it would have taken a lot longer."

Deis hopes to identify some of the many structures taken on by a protein called gp41, which is located on the outside of HIV and, along with another protein called gp120, helps the virus invade cells. Many scientists have hypothesized that a drug that latches onto gp41 could prevent it from functioning and therefore stop HIV infection.

However, gp41 has proven a wily target, in part because it takes on so many shapes and is challenging to work with.

"Gp41 is a sort of unpleasant protein to work with because it is sticky," Deis said. "If you make it by itself, it likes to stick to everything, including itself, and it just becomes a big boogery mess."

She has worked with Deller and SLAC scientists on strategies for crystallizing and determining the structure of the troublesome protein, and for modifying the usual crystallography conditions in a way that could allow her to see multiple structures.

"The staff at SLAC have been extremely accommodating and helpful, especially with some of our weird requests," she said.

In addition to providing equipment and help, the MSKC serves as a hub. "Having people to bounce ideas off of is really helpful," Deis said. "Because there are different labs coming together, you



Undergraduate student Zachary Rosenthal loads protein samples onto the crystallization robot at the Macromolecular Structure Knowledge Center, which is in the basement of the Shriram Center.

are interacting with all sorts of different people."

Creating a bridge

The idea for MSKC originated at Stanford ChEM-H, an interdisciplinary institute focused on the chemistry of human health. ChEM-H director Chaitan Khosla, PhD, professor of chemistry and of chemical engineering, saw SLAC as a valuable and underused resource.

The institute provided seed grants to three proposed projects in 2013 to encourage more Stanford faculty to make use of SLAC facilities. But the ChEM-H members who helped design the grants quickly realized that the institute's impact would be small if it were only providing a few seed grants every other year. Instead, they reasoned, a center like MSKC could create a path to SLAC for a much larger number of faculty and projects.

MSKC is jointly supported by Stanford ChEM-H, SLAC and the School of Engineering, and supports faculty from any school.

Deller said the new facility has technology for each step of the process, starting with fermenters, incubators and bioreactors for the cell cultures that churn out molecules of interest. It also has equipment for purifying the molecules, and a crystallization robot for dispersing minuscule quantities of the purified molecule into lab plates. These plates contain a variety of different conditions — variable buffers, precipitants, different acidity levels, salts — to see which combination induces the molecule to form crystals. It's these crystals that are probed using high-intensity X-rays at



Marc Deller, who heads the center, inspects bacterial cultures expressing proteins targeted for crystallization trials.

SLAC probe to reveal atomic structures.

"The crystallization step would be really time-consuming without the robot," Deller said. Doing it by hand requires significantly higher quantities of the molecule, he added.

MSKC contains equipment to survey those lab dishes and scoop crystals into tanks of liquid nitrogen for transport to SLAC.

Then there's Deller, who's on hand to plan subsequent attempts if the first crystallization doesn't provide a clear structure.

"You don't usually get the structure back the first time," he said. "It is very much an iterative process. You need to have the knowledge to be able to figure out what to do next if you don't get the structure the first time."

MSKC is one of two knowledge centers funded in part by ChEM-H. The other, the Medicinal Chemistry Knowledge Center, assists faculty in constructing medically relevant molecules and drug candidates. Together, the two centers train students and faculty and support efforts to develop drugs and understand biological processes at a chemical level. ISM



The vials contain a potential drug, which Deller is helping to determine the molecular structure of.

Health disparities research center launched with \$11.5 million grant

By Kris Newby

A newly established center at the School of Medicine will focus on identifying genetic and biological markers that could be used to help reduce disease in minority populations in the United States.

The Stanford Precision Health for Ethnic and Racial Equity Center, known as the SPHERE Center, will be funded by a five-year, \$11.5 million grant from the National Institute on Minority Health and Health Disparities at the National Institutes of Health.

The center also will develop analytical tools for precision health, data sets and outreach programs that help accelerate the integration of treatments and interventions within target communities.

This NIH award is one of the first programs funded under President Barack Obama's Preci-

sion Medicine Initiative, which seeks to gain better insights into the biological, environmental and behavioral influences on diseases in the United States. This specific award targets socioeconomically disadvantaged and rural populations that experience a disproportionate share of many diseases and adverse health conditions.

"At Stanford Medicine, we are committed to ensuring that all populations benefit from the precision health revolution," said Lloyd Minor, MD, dean of the School of Medicine. "Through this new center, we are honored to contribute to the elimination of health disparities as we lead the transformation of medicine away from after-the-fact diagnosis to prediction and prevention."

Mark Cullen, MD, professor of medicine and director of the Stanford Center for Population Health Sciences, said the award "is a great vote of

confidence for Stanford's precision health initiative. It also underscores our expanding commitment to applying the great discoveries from our labs to serve the needs of the community, a major agenda for population health sciences."

Cullen and Yvonne Maldonado, MD, professor of pediatrics and of health research and policy, will lead the new center.

"The SPHERE Center will bring together outstanding investigators from across the School of Medicine to address fundamental questions about health and disease among minority populations," Maldonado said. "These populations are often underrepresented in traditional clinical research, and this center is positioned to address this disparity."

Initial projects

The center is initially funding three projects.

Technique could help identify patients who would suffer chemotherapy-induced heart damage, researchers say

By Krista Conger

Cancer patients who receive a particular type of chemotherapy called doxorubicin run a risk of sustaining severe, lasting heart damage. But it is not possible to predict who is likely to experience this serious side effect. It is also unknown exactly how the drug damages heart muscle.

Now, researchers at the School of Medicine have shown that heart muscle cells made from the skin cells of breast cancer patients who suffered cardiac side effects after receiving doxorubicin respond more adversely to the drug than cells made from patients who did not.

These cells provide researchers with a sorely needed platform to study the effects of doxorubicin exposure on human heart muscle cells, and may allow them to one day predict which patients should avoid the drug. Until now, researchers have relied primarily on animal models to investigate the phenomenon because heart muscle tissue is difficult to obtain from living patients.

“In the past, we’ve tried to model this doxorubicin toxicity in mice by exposing them to the drug and then removing the heart for study,” said Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute and a professor of cardiovascular medicine and radiology. “Now we can continue our studies in human cells with iPS-derived heart muscle cells from real patients. One day we may even be able to predict who is likely to get into trouble.”

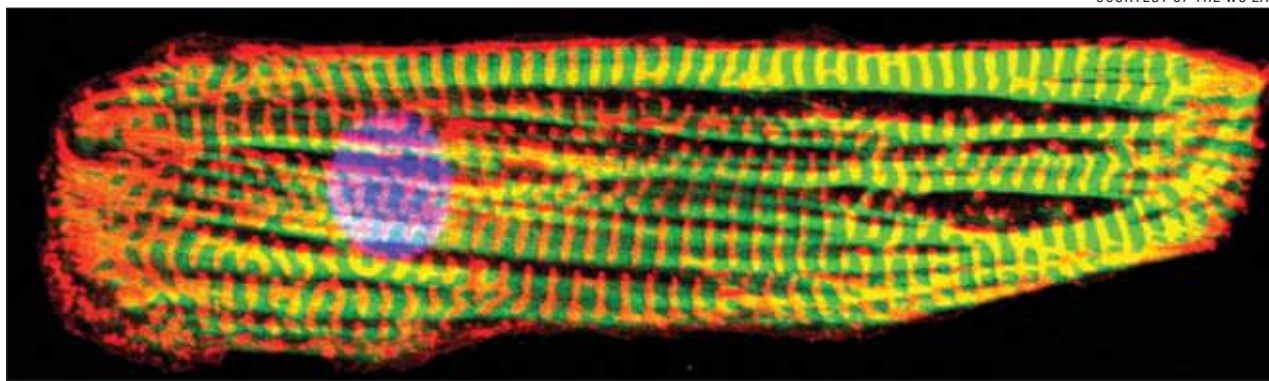
Wu, who also holds the Simon H. Stertzler, MD, Professorship, is the senior author of a study describing the work. The study was published online April 18 in *Nature Medicine*. Paul Burrige, PhD, a former instructor of cardiovascular medicine at Stanford, is the lead author of the study. Burrige is now an assistant professor of pharmacology at Northwestern University.

The research relies on induced pluripotent stem cells, or iPS cells, derived from patients’ own skin cells to make heart muscle cells. IPS cells are stem cells that can be coaxed to develop into nearly any tissue in the body. The technique gives researchers access to a variety of human cell types, such as brain and heart muscle cells, that are typically difficult to obtain for study.

Toxic side effect

About 8 percent of cancer patients treated with doxorubicin will experience heart damage, which can be severe enough to require a heart transplant. The failing heart function is due to the death of the cells in the organ’s muscle tissue. This dilemma places patients in a medical Catch-22, having been cured from cancer but later suffering heart disease as a result of the chemotherapy. Advanced prediction of which patients are susceptible to doxorubicin’s heart damage would greatly benefit cancer patients.

For the study, the researchers collected skin cells from 12 women, eight of whom had been treated at Stanford for breast cancer. Four of the eight had experienced heart damage in response to the drug while the other four did not. The other group of four women served as healthy control subjects. The researchers used the study participants’ own skin cells to create iPS cells, which they then grew in the lab into heart muscle cells.



COURTESY OF THE WU LAB

A heart-muscle cell made from an induced pluripotent stem cell, a type of cell that can be coaxed to develop into nearly any tissue in the body.

“We found that cells from the patients who had experienced doxorubicin toxicity responded more negatively to the presence of the drug,” said Burrige. “They beat more irregularly in response to increased levels of doxorubicin, and we saw a significant increase in cell death after 72 hours of exposure to the drug when we compared those cells to cells from healthy controls or patients who didn’t have heart damage.”

Some researchers have proposed that the particular sensitivity of heart muscle cells to the drug might be because they have more mitochondria than other cells in the body. Mitochondria serve as a cell’s energy factories, and continuously beating heart muscle cells need a lot of energy throughout their lifetimes. But they also produce small amounts of damaging molecules called reactive oxygen species as a byproduct of this energy-making process, and these molecules can harm cell membranes and DNA.

Mitochondrial mystery

The researchers found that the doxorubicin-sensitive cells experienced higher levels of DNA damage and of reactive oxygen species in the presence of doxorubicin.

These cells were also significantly more likely than cells from healthy controls or from patients who didn’t sustain heart damage to initiate a program of cellular suicide, which can be triggered by damage to the mitochondrial membrane. But the researchers made another telling discovery.

“We had assumed, based on our hypothesis, that the doxorubicin-sensitive cells would experience a more severe loss in mitochondrial capacity,” said Burrige. “And that was true. But we also observed that cells

made from patients who had experienced damage appeared to have slightly different baseline mitochondrial function even before the drug was applied.”

It is possible that heart muscle cells from these patients are fundamentally different than others, perhaps due to genetic variation, according to the researchers. This genetic difference could cause their heart muscle cells to respond negatively to doxorubicin.

The next step is to learn more about what causes the sensitivity, which the Stanford researchers hope to do by combining their studies of the iPS-derived cells with existing genome-wide association studies attempting to pinpoint DNA mutations that might cause compro-

mised heart function.

“Doxorubicin and other similar drugs are used to treat many types of cancers, including lymphomas and leukemias,” said Melinda Telli, MD, assistant professor of oncology at Stanford. Telli is a co-author of the study and helped recruit breast cancer patients for it. “But we don’t want to cure any of these patients of their cancers only to leave them with another life-threatening problem.”

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 co-authors are postdoctoral scholars Yong Li, PhD, Haodi Wu, PhD, Sang-Ging Ong, PhD, Alexandra Holmstrom, PhD, and Alex Chang, PhD; instructors Elena Matsa, PhD, Antje Ebert, PhD, and Michael Coronado, PhD; graduate student Arun Sharma; assistant professor of cardiovascular medicine Joshua Knowles, MD, PhD; associate professor of medicine Ronald Witteles, MD; professor of microbiology and immunology Helen Blau, PhD; professor of pediatric cardiology Daniel Bernstein, MD; and professor of bioengineering, of genetics and of medicine Russ Altman, MD, PhD.

The research was funded by the National Institutes of Health, the California Institute of Regenerative Medicine, the American Heart Association, a Dixon Translational Research Grant Young Investigator Award, the Muscular Dystrophy Association and the Burroughs Wellcome Fund.

The Stanford Department of Medicine and the Stanford Cardiovascular Institute also supported the work.

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Joseph Wu

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One will look for rheumatoid arthritis biomarkers among members of a Lakota Sioux tribe in South Dakota. It will be led by Michael Snyder, PhD, professor and chair of genetics.

Another will be led by Thomas Robinson, MD, professor of pediatrics and of medicine. His team will quantify metabolic and biomolecular differences of Latino youth to gain insights into the prevention and treatment of excessive weight gain and diabetes within this population.

The third will develop best practices for communicating genetic cancer risks to Latinos and Asian Americans. VJ Periyakoil, MD, clinical associate professor of medicine, will study responses of Latino and ethnic Chinese families when they receive genetic risk information about cancer. Her team will analyze the quality and content of communication between clinicians and patients over a one-year period to determine what health decisions are made based

on this information and how long-term outcomes might be improved.

To enable these studies, the center will work with 13 community-based organizations around the country.

Rhonda McClinton-Brown, MPH, executive director of the Center for Population Health Sciences’ Office of Community Engagement, will lead efforts to engage racial, ethnic and low-income communities in these studies. Her team will also align researchers, partner organizations and key stakeholders to accelerate the translation of these research findings into strategies that directly decrease health disparities.

The center will fund pilot projects starting in 2017.

Additional support for the center comes from Spectrum, the Stanford Center for Clinical and Translational Research and Education, which is funded by an NIH Clinical and Translational Science Award. ISM

NORBERT VON DER GROEBEN



Yvonne Maldonado and Mark Cullen will lead a new NIH-funded center aimed at improving the health of underserved ethnic and racial groups.

■ OBITUARY Gerald Friedland, former chief of Palo Alto VA, dies at 82

By Jennie Dusheck

Gerald Friedland, MD, a professor emeritus of radiology at the School of Medicine, died April 2 in Los Gatos, California. He was 82.

Friedland was also the former chief of what is now the Veterans Affairs Palo Alto Health Care System and a fellow of the Royal College of Physicians of Edinburgh. He received a Lifetime Achievement Award from Stanford and organized the first Pioneering Women in Medicine conference in 2000.

Friedland was born in Pretoria, South Africa, the son of Elizabeth Friedland and Garson Friedland, MD, a founding father of the Radiological Society of South Africa. Gerald Friedland led a career as a clinical radiologist, researcher and administrator. He authored or co-authored more than 100 medical articles and 35 book chapters and contributed to four books.

A formal and reserved man, Friedland was remembered by family members and colleagues as ethical, generous and devoted to research, teaching and mentoring.

From London to Palo Alto

After earning a medical degree from University of Pretoria, Friedland began a series of residencies in Scotland, Cambridge and London. By 1964, he had taken a post at London's Great Ormond Street Hospital for Sick Children.

In part because his wife Miriam "Micki" Friedland, MD, was allergic to the mold in old English houses, the couple began thinking about moving to the United States. Stanford was expanding its radiology department and, after applying for a position there, he learned that a young Stanford professor of radiology named Leslie Zatz, MD, happened to be in London on sabbatical.

The two men got together. "I was very impressed with him," Zatz recalled in an interview. "He was enthusiastic and well-trained." In 1967, the Friedlands moved to Palo Alto, and Friedland joined the faculty at Stanford as an assistant professor of radiology.

In the 1980s, Friedland succeeded Zatz as chief of what was then called the Palo Alto VA Medical Center and served in that position until his retirement in 1992 at age 59.

A passion for research

In Friedland's early years, his clinical focus was on pediatric radiology and radiologic gastroenterology, but he took increasing interest in urology and re-

search. He developed a way to use ultrasound to image the urethras and prostates of patients with spinal cord injuries, and also settled a debate about the structure of the esophagus.

"When he was pursuing something, he didn't give up. He was dogged and kept at it until he got the best answer he could," said Zatz.

In 1974, while on sabbatical at the University of California-Davis, Friedland became interested in the early development of the anus and rectum in human embryos. Friedland and renowned pediatric surgeon Pieter de Vries, MD, showed that human embryos do not form a cloaca, as previous researchers believed. The cloaca — found in birds, for example — is a single exit from the body for the urinary, digestive and reproductive tracts, instead of separate exits as most mammals have.

Friedland and de Vries showed that early human embryos skip the formation of a cloaca and form a rectum and an anus in the eighth week after fertilization.

A change of heart

At 51, Friedland suffered a heart attack that changed his life. "He became a big proponent of healthy eating," his daughter Jenny Tender, MD, said. "He knew about trans fats years before anyone else was talking about them." And he made a conscious effort to be less intense and more Type B, said Tender.

Friedland and work had always been like two sides of the same coin. "My dad grew up in this formal, British, South African home," Tender recalled. "He would literally not answer the door without his shoes on. He was pretty reserved, and for most of his life he worked like crazy, getting up every morning at 4:30 a.m." Although he loved and cared for his family deeply, his passion was his work, family members said.

Matilde Nino-Murcia, MD, an emeritus professor of radiology at Stanford whom Friedland mentored when she was younger, said Friedland was always curious and excited about learning, and a relentless worker. He always seemed to have time for one more thing and assumed others did, too, she said. One Tuesday, she said, she gave him a paper she'd been working on, thinking he'd return it in a few days and that she would finish it that weekend. Instead, Friedland read the whole paper

the same day. "He was very intense about things like that," she said.

While co-authoring his 2000 book *Medicine's 10 Greatest Discoveries*, Friedland was struck by how many women involved in major discoveries remained unknown. He came to believe that "women were being left out and not acknowledged for what they did," said Micki Friedland.

To help, he organized a conference at Stanford in 2000 called the Pioneering Efforts of Women in Medicine and the Medical Sciences, which in turn led to publication of the 2015 book *Pioneering Women in Medicine and the Medical Sciences*, which he co-edited.

Friedland eventually developed Alzheimer's disease with Parkinson's-like symptoms that made it difficult for him to walk. Although he suffered, said Micki Friedland, he never grumbled or complained. Instead, the once-obsessive worker preferred to sit peacefully. "Alzheimer's is a horrible disease," she said. "It robs people of so much."

Generous with time, credit

Friedland was a famously fair and attentive mentor to generations of residents, sharing both the actual work and the credit, said Nino-Murcia. "He took such pleasure in helping younger doctors," she said, also recalling how both Friedlands helped medical students from other countries, checking to make sure they had found a place to live, that their kids were in good schools and that they were settling in.

Nino-Murcia said Friedland was most proud of his daughters and his basic research, particularly the embryological work he did with Peter de Vries. It was, she said, "exquisite research." When he thought about that, she said, "his face would just be smiling."

"He was unbelievably generous," Tender said. "He would cook for people, and he wrote such sweet poems for my mom."

In addition to his wife, Friedland is survived by a brother, Lionel Friedland, and sister, Myrtle Todes; daughters Jenny Tender and Lucille Friedland; son-in-law Lenny Tender; and his three granddaughters, Alyssa, Gabrielle and Lily.

The family requests memorial donations to the Fisher Center for Alzheimer's Research. **ISM**



Gerald Friedland

McNutt discusses leadership lessons

By Becky Bach

In a talk on campus April 18, Marcia McNutt, PhD, shared lessons she's learned from leading top U.S. scientific institutions, including the journal *Science*, where she's currently the editor-in-chief.

McNutt's talk was part of the Dean's Lecture Series at the School of Medicine, and Dean Lloyd Minor, MD, who introduced her, said he was in part motivated to invite her to speak after they shared a six-hour ride through China in a "marginally air-conditioned bus."

"I can tell you she maintains good humor even under stressful conditions," Minor said, adding that the school was "honored and thrilled" to welcome her back to Stanford. (McNutt previously was a professor of geophysics at the university.)

Speaking to a large audience in Berg Hall, at the Li Ka Shing Center for Learning and Knowledge, McNutt offered three leadership lessons. "Much of what I learned about leadership was formed in the crucible of crisis," she said.

Budgetary crisis

The first example stemmed from a budgetary crisis during the post-9/11 recession, when she led the Monterey Bay Aquarium Research Institute. Despite a plummeting stock market, under McNutt's leadership the organization was able to avoid layoffs by developing a plan that focused on its core mission, which included conducting high-risk research. Importantly, the budget and plan were created by staff members, who were motivated to protect their jobs and were more likely to support a budget they had helped create, McNutt said.

As director of the U.S. Geological Survey, McNutt said one of her greatest challenges was managing efforts to deal with the Deepwater Horizon oil spill in the Gulf of Mexico in 2010. There, she needed to unite a diverse



"Much of what I learned about leadership was formed in the crucible of crisis," Marcia McNutt said in a talk at Stanford on April 18.

team of industry and government scientists, engineers and technical experts — all of whom had differing backgrounds and working styles and were reluctant to trust one another, McNutt said.

"The trick was to use their diversity as a strength," McNutt said. She tapped each team member's individual talents, using their expertise and wide-ranging opinions to reach the best solution quickly. "Especially in times of crisis, diversity matters," she said. "I can't emphasize diversity enough."

Finally, McNutt described the steps she took as editor-in-chief of *Science* to restore the credibility of scientific research following a series of high-profile scandals, including the fraud committed by South Korean researcher Hwang Woo-Suk, DVM, PhD, and the misconduct by stem-cell biologist Haruko Obokata, PhD.

These incidents, among others, prompted a wave of reforms at many top journals, including *Science*, to boost transparency and ethics. "Nothing matters more

Entwistle

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of the biomedical revolution in precision health to predict, prevent and treat disease as never before."

Prior to joining UUHC, Entwistle served as senior vice president and chief operating officer, as well as senior vice president of operations, for the University of Wisconsin Hospital & Clinics. Previously he was vice president of professional services and joint venture operations at City of Hope National Medical Center, where he also served as president and chief executive officer for oncology management services. He earned a master's degree in health services administration at Arizona State University and is a graduate of Brigham Young University.

"At this transformative time in health care, Stanford continues to raise the bar," said Entwistle. "I am thrilled to be joining a premier institution on the leading edge of discovery, education and clinical care. I look forward to working with the Stanford Health Care board, executive team, physicians and staff, as well as with partners at the Stanford School of Medicine and Stanford Children's Health, to provide outstanding care and outcomes matched by exemplary patient experience." **ISM**

than a good reputation in science," McNutt said. "Always take the high road and strive for openness and transparency."

That lesson is challenging because it will mean problems in research will increasingly be identified, she said. "We are going to have to live with that, because that is what is best for science," McNutt said. "The only antidote is to do really good science to begin with."

McNutt, who is the first woman to serve as editor-in-chief of *Science* since it was founded in 1880, will leave the journal in July to lead the National Academy of Sciences. She will be the first female leader of the academy since it was founded in 1863. **ISM**

Cell

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tumorous cells, and secreting copious signaling substances that spur further attack-mode action.

If it weren't for Tregs, this chain reaction might go unchecked, resulting in chronic inflammation, said Weyand. That's what begins to happen in many people as they grow older. As we age, our immune response tends to grow both hyperactive and unfocused, like a car with lousy brakes, a distracted driver and a brick on the gas pedal. "The aging immune system becomes less focused — less capable of defending against cancers and infections or responding robustly to vaccinations — and much more inflammatory," Weyand said.

CD4 Tregs and CD8 Tregs

Tregs have long been known to exist. But until recently, the only ones known belonged to a category of immune cells called CD4 T cells. These cells have earned their nickname as "helper T cells" by participating in the immune response's expansion, as opposed to contraction, phase. But CD4 Tregs suppress the activation and proliferation of helper T cells by secreting anti-inflammatory substances, for example, or by soaking up growth factors.

In work published in the *Journal of Immunology* in 2012, Weyand and her colleagues identified a set of Tregs hailing from a different category of T cells called CD8s. The CD8 Tregs — which, analogous to CD4 Tregs, account only a small fraction of all CD8 cells (also called "killer T cells" because they directly attack infected and cancerous cells) — differ in key respects from their CD4 counterparts, the helper T cells. For starters, the two cell types can be distinguished by the differential presence,

on their surfaces, of proteins respectively designated CD8 and CD4.

In the new study, Weyand and her colleagues found many more differences. Unlike CD4 Tregs, which circulate freely throughout the bloodstream and tissues, CD8 Tregs preferentially take up residence in lymph nodes, the spleen and other regions, where huge reserve armies of potentially warlike helper T cells either stand at ease or are proliferating and preparing to enter circulation in search of cancerous or infected tissues. This proximity puts the CD8 Tregs in a position to stamp out helper T cell activation early on.

Subduing helper T cell activity

Further experiments demonstrated that CD8 Tregs manufacture copious amounts of an enzyme called NOX2, which they package into tiny membrane-bound packets and transfer to the surfaces of abutting helper T cells. These NOX2-laden packets are taken up by the helper T cells. Inside their new home, the enzymes produce large volumes of highly reactive signaling substances that dial down helper T cells' activation and proliferation.

There is no evidence to date that CD4 Tregs share this mechanism, whose effect is long-lasting. Contact between CD8 Tregs and helper T cells in early stages of activation shuts down the helper cells' activity and reduces their proliferation by half or more, even several days after the CD8 Tregs have been removed.

Transferring NOX2 alone onto activated helper T cells also produces this effect.

Obtaining samples of healthy individuals' blood from the Stanford Blood Center, the investigators observed that CD8 Tregs were only about half as common in blood from people ages 60 or older as in blood from 20- to 30-years-

olds. Not only CD 8 Tregs' numbers but their ability to suppress helper T cell proliferation decline with advancing age, the researchers found. Laboratory experiments traced this to a drop in NOX2 production by older donors' CD8 Tregs.

Next, the researchers focused on a cluster of disorders collectively called vasculitides, auto-inflammatory diseases in which T cells, in combination with other immune cells called macrophages, gang up and attack vascular tissue. Both Weyand and study co-author Jorg Goronzy, MD, professor of medicine, frequently see patients with vasculitis at Stanford Health Care's Immunology and Rheumatology Clinic.

"It's never good to have your vascular tissue attacked, and it's especially dangerous when the vessels under attack are large arteries such as the aorta," said Weyand. An injured artery can burst or become occluded. Either event can be life-threatening.

A potent form of vasculitis

One particularly potent and poorly understood form of vasculitis is giant-cell arteritis. In GCA, which affects large blood vessels, inflammation is so fierce it drives macrophages to fuse and form so-called giant cells.

Fortunately, CGA is also rare. "Its greatest incidence — about one in 10,000 new cases per year — is in Iceland," said Weyand, a world-renowned expert on the disorder. "Curiously, no one below age 50 ever gets it, and until they do these patients appear completely healthy. Even after they come down with it, they're no more susceptible to cancer or viral infections than healthy people."

The new study showed why: GCA patients' immune brakes, their CD8 Tregs, are shot, leaving helper T cell populations in their lymph nodes relatively unpoliced. Comparisons of their blood

with that of age-matched healthy control subjects and patients with two other autoimmune diseases — psoriatic arthritis and small-vessel vasculitis — spotlighted a severe deficit among GCA patients in NOX2-producing CD8 Tregs. There was no such deficit among the patients with the two other disorders or in the healthy control subjects.

"This tells us that the deficit in NOX2-producing CD8 Tregs is specific to GCA, not just driving or driven by inflammation," said Weyand. "That's good news for our patients who have this disease, which has been an enigma. Now we know something about what's causing it."

The discovery, in this study, of NOX2 on the surface of CD8 Tregs — but not on other T cell types — makes them much easier to identify and count, Weyand said. She and her associates are taking advantage of the new-found biomarker to tally CD8 Tregs in patients with age-associated disorders now understood to be driven by chronic inflammation, such as coronary artery disease and Alzheimer's and Parkinson's diseases, to see if CD8 Treg deficits underlie some of these conditions' disease pathology — and whether they may be amenable to potential NOX2-restoring treatments.

The team's 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 co-authors of the study are postdoctoral scholars Tsuhoshi Shirai, MD, PhD, and Vinyin Li, PhD; research associates Jihang Ju, PhD, and Zhen Yang, PhD; and associate professor of biomedical data science Lu Tian, SciD.

The study was funded by the National Institutes of Health, and the Govenar Discovery Fund. Stanford's Department of Medicine also supported the work. **ISM**

Drinking

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in *Addiction*. Humphreys is the senior author. The lead author is psychiatric medicine resident Agnes Kalinowski, MD, PhD.

Kalinowski and Humphreys surveyed the definitions of "standard drink" and low-risk drinking in each of 37 countries around the world. They found that, although the World Health Organization defines a standard drink as one containing 10 grams of alcohol, most countries have their own ideas. A standard drink in Austria, for example, contains 20 grams of alcohol, while those in Iceland and the United Kingdom contain 8 grams. The United States splits the difference, with a standard drink of 14 grams of alcohol, which is roughly the amount in a 12-ounce bottle of beer or a 5-ounce glass of wine.

Different definitions of low risk

Many countries also provide different definitions of low-risk drinking — or the amount of alcohol that can be consumed per day or week without experiencing adverse health effects. Men and women in Australia are told they should drink no more than 20 grams each day; American women are allotted 42 grams per day but no more than 98 grams per week. In contrast, men in the United States are told they can safely drink 56 grams per day and up to 196 per week. The upper weekly limit for men in Poland is substantially higher, at 280 grams per week.

The variability seen by the researchers reflects the need for more study about responsible alcohol consumption and also the differences in cultural attitudes among countries, according to



Keith Humphreys is senior author of a paper that found that governmental guidelines for low-risk drinking vary widely.

Humphreys.

"More and more countries are trying to give their citizens guidelines about how much alcohol is safe to drink, and for whom," said Humphreys. "At the very least, we should know whether it's true that women should drink less than men. But even this is unclear.

"We've also learned that what constitutes a 'standard drink' in each country is far from standard, despite the WHO's recommendation. But in many cases these guidelines are adopted as public health policy and even printed onto alcoholic beverages without knowing whether people read them, understand them or change their behavior as a result."

The research was supported by the U.S. Veterans Health Administration.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. **ISM**

Autism event for parents, educators on May 7

By Erin Digitale

Parents who are raising a child with autism can struggle to piece together all the information they receive. News of possible therapies, novel brain-science discoveries and individual anecdotes about others' treatment experiences may leave them wondering: How could this help my child?

Lucile Packard Children's Hospital Stanford and Stanford Children's Health are here to help parents understand the puzzle. On May 7, the hospital will present its ninth annual Autism Spectrum Disorders Update, an event that gives members of the community a chance to learn about new autism research and therapies.

This year's conference includes keynote presentations by internationally renowned autism experts Catherine Lord, PhD, and Peter Mundy, PhD, in addition to Stanford researchers, including Vinod Menon, PhD, a professor of psychiatry and behavioral sciences.

Lord, professor of psychology at Weill Cornell Medical College, is a leading autism authority who is helping transform the way this disorder is diagnosed and treated. She will discuss the rationale and impact of the new diagnostic criteria for autism spectrum disorder that came into effect in 2013 with the publication of the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*.

Mundy, a professor of education and of psychiatry and behavioral sciences at University of California-Davis, will speak about a core autism deficit: lack of joint

attention. Many scientists theorize that this inability to gesture or talk with another person about an interesting object or event may underlie other problems in autism.

"We're excited about all parts of the program this year," said Antonio Hardan, MD, chief of the Division of Child and Adolescent Psychiatry at the Stanford School of Medicine and director of the Stanford Autism Center at Packard Children's. "It's great to be able to present our cutting-edge Stanford research, and we are especially glad to be bringing Dr. Lord and Dr.



Antonio Hardan

Mundy to Stanford in response to parents' interests."

In addition to the keynote presentations, Stanford autism experts will discuss a wide cross-section of topics, including new research findings in many areas of autism science from stem cell research to innovative clinical trials. The day will include breakout sessions with time for Q&A sessions with speakers. The complete program is online at <http://med.stanford.edu/autismcenter/events.html>.

The symposium is scheduled from 8:45 a.m. to 4:30 p.m. May 7 at the Li Ka Shing Center for Learning and Knowledge. (Registration and continental breakfast begin at 8:15 a.m.) Register online at <http://www.stanfordchildrens.org/en/service/autism/symposium>.

Parents, teachers, pediatricians, psychologists, caregivers and anyone with an interest in autism spectrum disorder are invited to attend. The \$125 registration fee includes the continental breakfast and a buffet lunch. **ISM**

Three students at medical school awarded Soros fellowships

By Kathleen Sullivan

Three students at the School of Medicine have received 2016 Paul & Daisy Soros Fellowships for New Americans.

Binbin Chen, Veronica Manzo and Suhas Rao are among the six current Stanford students and one alumna to be awarded the fellowships, which support graduate studies with as much as \$90,000 over two years for tuition and living expenses.

BINBIN CHEN will use his fellowship to support his MD and PhD (genetics) studies at the medical school, where he is developing bioinformatics tools to understand patient responses to immunotherapy. He is working in the lab of Russ Altman, MD, PhD, a professor of bioengineering, of genetics and of biomedical informatics, and in the lab of Ash Alizadeh, MD, PhD, an assistant professor of oncology.

Chen was born in Fuzhou, a city of more than 7 million people in southeast China. He joined his mother in the United States when he was 18 years old. She had settled in Georgia after fleeing China seven years earlier following her husband's arrest and imprisonment.

Chen earned a bachelor's degree in biomedical engineering at the Georgia Institute of Technology in 2013. As a sophomore, he was the first-author of a paper published in the *Journal of Translational Medicine*. As a senior, he helped organize the first LGBT graduation reception at Georgia Tech, an event covered by a National Public Radio station in Atlanta.

After graduating, Chen spent a year in Johannesburg, South Africa, investigating a bimolecular method to assess drug adherence by HIV patients. While there, he observed the social stigma against HIV patients and those who identified as lesbian, gay, bisexual or transgender.

At the medical school, Chen is the co-president of LGBT Meds, an activist and social organization dedicated to raising awareness of queer health issues and promoting equal social and political rights for LGBT people. He also volunteers at the Pacific Free Clinic, which was established by Stanford medical students to address the unmet health care needs of immigrants with limited English proficiency by offering free health care services and education in a linguistically and culturally appropriate manner.

VERONICA MANZO will use the fellowship to support her medical studies.

Manzo was born in Riverside, California, to Mexican parents. Her family emigrated from small towns in Michoacán and Jalisco to seek opportunity and jobs as farmworkers.

She earned a bachelor's degree in neurobiology in 2013 at Harvard, where she minored in global health and health policy. At Harvard, she conducted research on glioblastoma multiforme, a deadly brain tumor, and co-authored a paper titled "Passenger deletions generate therapeutic vulnerabilities in cancer," which was published in *Nature* in 2012.

After graduating, she worked on research projects at the Dana-Farber Cancer Institute and at the Broad Institute of Harvard and MIT to build her knowledge of genetics. She also volunteered for Global Oncology, a community dedicated to alleviating suffering and providing the highest quality cancer care to people in resource-limited settings.

At the medical school, she has been a member of the lab of Ami Bhatt, MD, PhD, an assistant professor of medicine and of genetics. Manzo has tailored her coursework to focus on cancer biology and community health.

Last summer, she helped implement preventive medicine programs at the Ravenswood Family Health Center in East Palo Alto, which provides health care to all patients, regardless of their ability to pay or immigration status. She has also served as co-chair of the Latino Medical Student Association.

SUHAS RAO will use the fellowship to support his medical studies and his doctoral studies in biomedical science.

Rao, who was born in Massachusetts, is the son of Indian immigrants who came to the United States in the 1980s.

He earned a bachelor's degree in applied mathematics at Harvard in 2012. As an undergraduate, he worked at the Broad Institute of Harvard and MIT, where he was inspired by the potential of the "genomics revolution" to drive a new age in precision medicine and patient care.

However, while working at the Harvard Square



Binbin Chen



Veronica Manzo



Suhas Rao

Homeless Shelter, Rao realized that revolutions in health care weren't particularly useful if they weren't accessible to those who need them most. His desire to work at the forefront of biomedical research and to translate this research into clinical practice led him to a career as a physician-scientist.

Rao continued his research on the three-dimensional structure of the genome at the Broad Institute and the Baylor College of Medicine, resulting in being first co-author of publications in *Cell* and in the *Proceedings of the National Academy of Sciences*.

That work resulted in the highest resolution maps of the 3-D genome to date and revealed numerous structural principles of genome folding. It was covered on National Public Radio and in *Time*, *Forbes*, *The Atlantic* and *Scientific American*.

Rao hopes to tackle the fundamental problem of deciphering the information contained in the genome and to translate that into more precise modalities of patient care.

A total of 30 Soros Fellowships for New Americans were given to students nationwide. The fellows can study in any degree-granting graduate program in any field at any university in the United States. Immigrants and the children of immigrants, they are selected on the basis of merit. The specific criteria emphasize creativity, originality, initiative and sustained accomplishments.

The late Paul and Daisy Soros, Hungarian immigrants and American philanthropists, established the program in 1997 and awarded the first fellowships the following year. The couple wanted to "give back" to the country that had given so much to them and their children, to address an unmet need by assisting "young New Americans at critical points in their educations" and to call attention to the extensive and diverse contributions of immigrants to the quality of life in the United States. **ISM**

OF NOTE

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

DANIEL PALANKER, PhD, professor of ophthalmology, has been awarded the Bressler Prize in Vision Science by the Lighthouse Guild, a nonprofit organization that serves the blind and visually impaired. The award recognizes a scientist whose leadership, research and service have led to advances in the understanding and treatment of eye diseases. Palanker has developed several optical and electronic devices to treat ocular diseases, including a wireless implant for restoration of sight lost because of retinal degenerative diseases.

STEPHEN QUAKE, PhD, was awarded the 2016 Raymond and Beverly Sackler Prize in Convergence Research by the National Academy of Sciences. The honor, which includes a \$350,000 cash prize, recognizes advances in convergence research, the integration of two or more of the disciplines of mathematics, physics, chemistry, biomedicine, biology, astronomy, earth sciences, engineering and computational science.

Quake was recognized for his contributions to human health, including the development of noninvasive diagnostic procedures and biological devices analogous to electronic circuits. He is the Lee Otterson Professor in the School of Engineering and professor of bioengineering and of applied physics.

EILA SKINNER, MD, professor and chair of urology and the Thomas A. Stamey Research Professor in Urology, was elected a trustee of the American Board of Urology. The board establishes and maintains standards of certification for urologists. Skinner's six-year term began in February. A specialist in urologic oncology, she focuses on the medical and surgical treatment of bladder cancer and on urinary tract reconstruction.

LINDA YIP, PhD, a senior research scientist, was given the young investigator award by the Network of Pancreatic Donors with Diabetes. The award recognizes an early-career researcher who has contributed outstanding work on Type 1 diabetes. Yip's research focuses on the role of gene splicing in the pathogenesis of Type 1 diabetes and on identifying gene-expression biomarkers of disease risk and progression. **ISM**



Daniel Palanker



Stephen Quake



Eila Skinner



Linda Yip

Drug development expert to speak at medical school graduation

Faculty member Peter Kim, PhD, a biochemist known for his innovative work in developing and shepherding drugs to market, will be this year's speaker at the School of Medicine's diploma ceremony.

The ceremony will be held from 1-3 p.m. June 11 on Alumni Green, next to the Li Ka Shing Center for Learning and Knowledge. No tickets are required.

Kim, who earned a PhD in biochemistry at Stanford in 1985, returned to the university in 2014 as a professor of biochemistry. He is also the Virginia & D.K. Ludwig Professor of Biochemistry and a member of ChEM-H, an interdisciplinary institute focused on the chemistry of human health. His research at Stanford includes efforts to create an HIV vaccine.

As the president of Merck Research Laboratories for 10 years, he led teams of chemists, biologists, engineers, statisticians and clinicians. Among the many products launched under his watch was a vaccine targeting human papilloma virus, the causative agent of cervical cancer, as well as drugs with novel mechanisms of action to treat Type 2 diabetes, HIV and the hepatitis C virus. Kim also oversaw the development of vaccines against rotavirus and shingles.

The co-author of more than 130 peer-reviewed scientific articles, Kim holds 17 patents and is a fellow of the American Academy of Arts and Sciences and of the American Association for the Advancement of Science. He also is a member of the National Academy of Sciences, the National Academy of Medicine and the National Academy of Engineering. He is one of only 20 people to have membership in all three national academies.

More information about commencement is available at: <http://www.med.stanford.edu/md/student-life/events/commencement.html>. **ISM**



Peter Kim