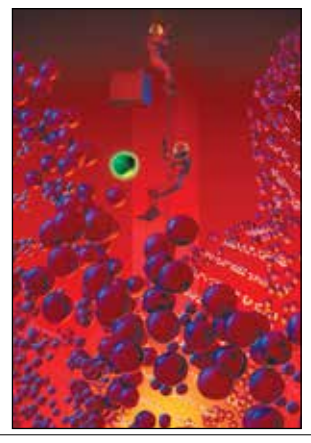
INSIDE STANFORD MEDICINE

Volume 11, No. 12 ■ June 24, 2019 ■ Published by the Office of Communication & Public Affairs



The new issue of *Stanford Medicine* magazine highlights the joy of fundamental research.

Page 5

Grads urged to embrace lifelong learning

By Julie Greicius

STEVE FISCH

At the School of Medicine's graduation ceremony on June 15, 180 students walked across the stage to receive their diplomas as family and friends cheered their accomplishments.

Embracing the outlook of a "student for life" is the best way to adapt to the inevitable changes, challenges and opportunities ahead, Stanford Provost Persis Drell, PhD, told School of Medicine graduates on June 15.

"The goal of your training was not to fill you up with knowledge and send you out into the world. The goal of your training at Stanford was to help you learn and embrace being a student for a lifetime," she said. "My advice to you: In a world that encourages increasing specialization, hold on to that sense of being a student."

A lifelong student herself, Drell is also the James and Anna Marie Spilker Professor in the School of Engineering and a professor of materials science and engineering and of physics. She is the former dean of the Stanford School of Engineering and the former director of the U.S. Department of Energy's SLAC National Accelerator Laboratory at Stanford.

Drell spoke at the medical school's 111th diploma ceremony, which was held on campus at the newly reopened Li Ka Shing Alumni Lawn. She was introduced by Lloyd Minor, MD, dean of the School of Medicine, who also spoke to faculty and graduating students and their families and loved ones.

The provost emphasized the importance of being able to adapt to uncertainty and change, and also stressed the graduates' role in advocating for and restoring trust in science. "Trust must be earned every day, in every interaction, with every person we come in contact with," she said. "In the coming years, you will have many opportunities to engender public trust and focus attention on the many ways science has improved and will continue to improve our lives."

'Another chapter'

The ceremony began with a performance by Dane Johansen, a cellist in the Cleveland Orchestra and sibling of Sara Johansen, a member of the 2019 graduating class. Johansen played the first movement of Bach's Suite in D Major for unaccompanied cello.

In his remarks to the graduates, faculty and guests, Minor (who, like Drell, is a cellist in his spare time) encouraged the graduates to anticipate unpredictable changes in their future, and to experience them as opportunities for growth. "Having an idea of what you want and how to get there is See GRADUATION, page 4

Stanford physicians train fire departments in latest emergency medicine techniques

By Susan Coppa

Contrary to popular opinion and most television shows, the first responders to reach the scene of a medical emergency aren't usually an ambulance crew but firefighter-paramedics. In fact, the majority of the calls fire departments respond to are medical.

Because of the crucial role that fire departments play in pre-hospital care, Stanford Health Care and the Stanford Department of Emergency Medicine have developed partnerships with nine local fire departments, including those in Palo Alto, Mountain View and Santa Clara, to ensure that first responders are trained in the latest emergency medical care.

RAFAEL CRUZ

Stanford emergency medicine physician Peter D'Souza (center) watches while Palo Alto firefighters Brian Tognazzi (left) and Yovan Sierra practice resuscitation techniques.

Typically, a single fire department will contract with one physician to serve as its medical director. The Stanford approach is different: Several faculty members in the Department of Emergency Medicine serve as the collective medical director for multiple fire agencies. The approach has yielded significant benefits, said Marc Gautreau, MD, clinical associate professor of emergency medicine and director of pre-hospital care at Stanford.

Individually contracted medical directors rarely provided onsite training to the firefighters because of the time involved in traveling to and coordinating with multiple fire stations. However, with a team of physicians to draw from, Stanford has been able to provide frequent, consistent training and ensure quick dissemination of new protocols and emergency procedures to stations throughout the peninsula, said Peter D'Souza, MD, clinical assistant professor of emergency medicine. See FIRE, page 6

Legalizing medical pot doesn't reduce rate of fatal opioid overdoses

SHUTTERSTOCK

By Mandy Erickson

Legalizing medical marijuana does not reduce the rate of fatal opioid overdoses, according to researchers at the School of Medicine.

The finding contradicts a 2014 study that legal-pot advocates, public officials and even physicians have touted as a reason to legalize marijuana. That study found lower rates of fatal opioid overdoses in the states that had legalized marijuana for medical purposes than in states where marijuana remained illegal.

The Stanford study, which revisited the issue after many more states had legalized medical marijuana, found no evidence of a connection between opioid deaths and the availability See MARIJUANA, page 7

Most metastatic colorectal cancers spread before diagnosis

By Krista Conger

Up to 80% of metastatic colorectal cancers are likely to have spread to distant locations in the body before the original tumor has exceeded the size of a poppy seed, according to a study of nearly 3,000 patients by researchers at the School of Medicine.

Identifying patients with early stage colorectal tumors that are born to be bad may help doctors determine who should receive early treatments, such as systemic chemotherapy, to kill cancer cells lurking far from the tumor's original location.

"This finding was quite surprising," said Christina Curtis, PhD, assistant professor of medicine and of genetics at Stanford. "In the majority of metastatic colorectal cancer patients analyzed in this study, the cancer cells had already spread and begun to grow long before the primary tumor was clinically detectable. This indicates that metastatic competence was attained very early after the birth of the cancer. This runs counter to the prevailing assumption that metastasis occurs late in advanced primary tumors and has implications for patient stratification, therapeutic targeting and earlier detection."

PAUL SAKUMA

Christina Curtis and her colleagues found that colon cancer tumors could potentially spread to other parts of the body much earlier than previously known. Identifying patients in whom early metastasis is likely could better guide treatment decisions.

Researchers and clinicians have assumed that cancers acquire the ability to metastasize through the gradual accumulation of molecular changes over time. These changes, the thinking goes, confer specific traits that eventually allow cancer cells to escape the surrounding tissue, enter the bloodstream and take up residence in new locations. In this scenario, metastasis, if it occurs, would be a relatively late event in the evolution of the primary cancer.

Curtis, who co-directs the molecular tumor board at the Stanford Cancer Institute, is the senior author of the study, which was published online June 17 in *Nature Genetics*. Postdoctoral scholar Zheng Hu, PhD, is the lead author.

Second-leading cause of cancer death

Colorectal cancer is the second-leading cause of cancer death in men and women combined in the United States. It metastasizes most often to the liver. Rarely, it metastasizes to the brain, where it is almost always fatal.

The initial changes to the genome that cause cancer are called driver mutations. The driver changes that jumpstart colorectal cancer are well-known, making it a good model to learn more about how and when the disease progresses. Curtis and her colleagues sought to reconstruct when metastasis occurred on a patient-by-patient basis and to identify its drivers by analyzing tumor-genome data.

Studying tumor biopsies, the researchers compared patterns of genetic mutations in the primary tumors of 23 patients with the patterns in their liver or brain metastases. They looked for similarities or differences between primary and metastatic cancers obtained from the same person. They then used those patterns to create a kind of evolutionary tree of each patient's cancer — similar to one a biologist might make to trace the evolution of an animal species from a single ancestor.

The trees the researchers pieced together indicated that in 17 of 21 patients (two of the original patients were excluded from the analysis), the metastatic tumors were started by just one cell, or a small group of genetically similar cells, that broke off from the primary tumor early in its development.

"The cells that formed the metastasis were more closely related to the ancestors of the primary tumor than its present-day relatives," Curtis said. "Moreover, the metastasis shared early drivers present in the 'trunk' of the evolutionary tree, but harbored few additional drivers. This suggested that these cancers acquired metastatic competence very early on during their growth."

To further pinpoint when metastasis occurred, Curtis and her team developed a computer program and statistical method to measure the time of metastatic spread relative to the size of the primary tumor in an individual patient. Their analysis provides the first quantitative evidence for early metastatic spread in human colon cancer — a pattern observed in virtually all cases they examined. However, Curtis noted that not all colorectal tumors will metastasize and that it will be important to also understand cellular processes that keep the cancer from spreading to other organs.

Curtis and her colleagues then took what they had learned and applied it to 938 people with metastatic and 1,813 people with nonmetastatic colorectal cancer whose medical histories were known and whose primary tumors had been profiled to identify genetic changes in known cancer-associated genes.

"We found that specific combinations of mutations were highly predictive of metastasis," Curtis said. For example, mutations in a gene called PTPRT, in combination with mutations in classic colorectal cancer driver genes, were almost exclusively found in patients with metastatic cancers.

Previous studies have shown that the loss of PTPRT function increases the activity of a protein called STAT3, which enhances cellular survival. The researchers speculate that inhibiting STAT3 might thwart tumor growth and metastasis.

Analyzing other cancers

Curtis and her colleagues are now working to learn whether specific molecular changes tilt the balance of metastasis in colorectal cancers toward the liver or the brain. They are also applying similar analyses to other types of cancers.

"The concept of early systemic spread has been controversial, due in part to the challenge of quantifying this process in the human system and the reliance on animal models," Curtis said. "These data indicate that metastasis can occur early in human colorectal cancer and highlights the critical need for the earlier detection of aggressive disease. New biomarkers based on specific combinations of alterations might enable the identification of potentially lethal colorectal tumors at an earlier stage so that they may be intercepted and appropriately treated, potentially with therapies directed against their specific aberrations."

Curtis is a member of the Stanford Cancer Institute and of Stanford Bio-X.

Other Stanford co-authors of the study are former senior research scientist Jie Ding, PhD; senior research scientist Zhicheng Ma, MD; instructors Ruping Sun, PhD, and Jose Seoane, PhD; visiting scientist J. Scott Shaffer, PhD; and clinical assistant professor of pathology Carlos Suarez, MD.

Researchers from the Medical University of Vienna, the University of Pisa, University of Padua and the University of Southern California also contributed to the study.

The research was supported by the National Institutes of Health, the American Cancer Society, the Wunderglo Foundation, the Emerson Collective Cancer Research Fund, the Innovative Genomics Initiative and the National Cancer Institute.

Curtis is a scientific adviser to Menlo Park-based GRAIL Inc. and holds stock options. She is a consultant for GRAIL and Genentech.

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

Researchers develop AI tool to help detect brain aneurysms

By Taylor Kubota

Doctors could soon get some help from an artificial intelligence tool when diagnosing brain aneurysms — bulges in blood vessels in the brain that can leak or burst open, potentially leading to stroke, brain damage or death.

The AI tool, developed by researchers at Stanford and detailed in a paper published June 7 in *JAMA Network Open*, highlights areas of a brain scan that are likely to contain an aneurysm.

"There's been a lot of concern about how machine learning will actually work within the medical field," said Allison Park, a graduate student in statistics and co-lead author of the paper. "This research is an example of how humans stay involved in the diagnostic process, aided by an artificial intelligence tool."

This tool, which is built around an algorithm called HeadXNet, improved clinicians' ability to correctly identify aneurysms at a level equivalent to finding six more aneurysms in 100 scans that contain aneurysms. It also improved consensus among the interpreting clinicians.

While the success of HeadXNet in these experiments is promising, the team of researchers — who have expertise in machine learning, radiology and neurosurgery — cautions that further investigation is needed to evaluate the generalizability of the AI tool prior to clinical deployment, given differences in scanner hardware and imaging protocols across different hospital centers. The researchers plan to address such problems through multicenter collaboration.

Combing brain scans for signs of an aneurysm can mean scrolling through hundreds of images. Aneurysms come in many sizes and shapes and balloon out at tricky angles. Some register as no more than a blip within the movielike succession of images.

Augmented expertise

"Search for an aneurysm is one of the most labor-intensive and critical tasks radiologists undertake," said Kristen Yeom, MD, associate professor of radiology and co-senior author of the paper. "Given inherent challenges of complex neurovascular anatomy and potential fatal outcome of a missed aneurysm, it prompted me to apply advances in computer science and vision to neuroimaging."

Yeom brought the idea to the AI for Healthcare Bootcamp run by Stanford's Machine Learning Group, which is led by Andrew Ng, PhD, adjunct professor of computer science and co-senior author of the paper. The central challenge was creating

See BRAIN, page 3

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
455 Broadway, 4th floor
Redwood City, CA 94063
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

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

STANFORD MEDICINE

5 QUESTIONS

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

Ensuring new Stanford Hospital's seismic safety

Seismologists can't predict when, where or how severe an earthquake will be, but the probability of the Bay Area getting severely shaken by one in the next 30 years is high. Seismic safety was the No. 1 driver for construction of the new Stanford Hospital set to open in the fall, said Bert Hurlbut, vice president of new hospital construction at Stanford Health Care. Under a stringent California building code, all hospitals must be able to remain operational after a major earthquake by 2030.

The new hospital was built to withstand a magnitude 8.0 quake. Structural engineers made that calculation based on the site's proximity to two major faults: the San Andreas and Hayward lines. The Hayward fault, which is 10 miles east of the hospital, poses the greatest danger. Scientists with the U.S. Geological Survey have described it as a "tectonic time bomb."

Writer Daphne Sashin asked Hurlbut about the strategies his team used to make the new hospital seismically safe.

1 What did you do to make the building earthquake-resistant?

HURLBUT: We used what's called a base isolation system. About 30 feet below ground level, we put huge steel and teflon coasters called isolators under the columns that support the building. They can slide as much as 3 feet in any direction, so that allows the building to shift up to 6 feet in an earthquake. The big isolators weigh 2.5 tons, and our humongous ones weigh 4 tons. Each one will take off a few million pounds of pressure from the weight of the building in an earthquake. The same system was used at the new Zuckerberg San Francisco General Hospital and the new Apple campus.

With Stanford providing the only Level I trauma center on the Peninsula, it's especially critical that the hospital be up and running to receive a large number of injured people in an emergency. It was just impractical to try to renovate the current hospital.

NORBERT VON DER GROEBEN

Bert Hurlbut says the new Stanford Hospital has been built to withstand an 8.0 earthquake because of its proximity to two major faults. The new hospital will open in the fall.

2 How do you make sure the building doesn't move too far?

HURLBUT: You build this big concrete bathtub, 4 feet larger all the way around your building, and that allows your building to move back and forth underground. It's like a moat.

The tough part is your utilities. You've got to get water into the building, sewage out, electricity in, medical gases in, natural gas in — all kinds of stuff. So every one of those pipes is fixed at the moat wall; they're tied to the concrete. This building's going to potentially move 6 feet, so you have to allow that pipe to be able to move 6 feet without breaking. On some of the larger pipes, like the 12-inch sewer pipes, that pipe might have to be 60 feet long to allow that 6 feet of movement. That means nothing can get in its way for 60 feet. It's not easy.

3 What other steps did you take to make the building earthquake-resistant?

HURLBUT: We've got a tremendous amount of piping above the ceiling, and all that piping has to be braced. If you just let it hang there, it's going to swing back and forth in an earthquake and start hitting things and breaking. And as soon as a water pipe breaks, you have to shut down your hospital. The amount of braces we have to put on piping and ductwork is unbelievable. I'd bet we have 10,000 braces, and to make them all fit is not an easy task.

Another difficult element was the dome, which is made of about 11,000 square feet of glass pieces above the atrium to allow natural light in. The glass sections are probably about an inch and a half away from each other, and it's caulked in between. That inch and a half allows the dome to deform during an earthquake. And there's a safety film of plastic so in case that glass breaks, it will not fall down and shower down on the people below it.

4 How does the team make sure all this is going to work?

HURLBUT: You build a portion of your building — you can see the exterior wall mockups on Welch Road — and you spray it with a lot of water, and then you push and pull on it and shake it, and a lot of things crack and deform, and then you spray water again, and it can't let water in after the earthquake. We did some minor tweaking to caulk and similar waterproofing elements to ensure a successful flood test.

All the equipment in the building has gone through a shake test. You take whatever you're testing — whether it's an electrical panel, a transformer or a computer-room air conditioner — and you affix it to a table, and it might be as big as a room. Then you turn a machine on and it starts shaking horizontally and vertically, vigorously. You sit back and say, "I don't want to get too close to that."

5 How long can the hospital operate if it's cut off from the city utility system?

HURLBUT: We have enough provisions that we can go four days without supplies from outside the hospital. We store water, food and diesel fuel for the generators and the boilers. And if the sewer pipes break, we can store sewage in five tanks below the ground.

As a Level I trauma center, we also need to be prepared to deal with mass casualties following a major earthquake. The parking structure can be converted for additional triage space and connects directly to the emergency department. The garage has four decontamination showers which will aid the ED crew to get mass casualties ready for their entrance into the hospital in the event the victims are soiled with hazardous materials. We also have Wi-Fi to allow staff to register and admit victims into the facility during a mass casualty event. **ISM**

Brain

continued from page 2

an artificial intelligence tool that could accurately process these large stacks of 3D images and complement clinical diagnostic practice.

To train the algorithm, Yeom worked with Park and Christopher Chute, a graduate student in computer science, on labeling clinically significant aneurysms detectable on 611 computerized tomography angiogram head scans.

"We labelled, by hand, every voxel — the 3D equivalent to a pixel — with whether or not it was part of an aneurysm," said Chute, who is also co-lead author of the paper. "Building the training data was a pretty grueling task, and there were a lot of data."

Following the training, the algorithm decides for each voxel of a scan whether there is an aneurysm present. The end result of the HeadXNet tool is the algorithm's conclusions overlaid as a semi-transparent highlight on top of the scan. This representation of the algorithm's decision makes it easy for the clinicians to still see what the scans look like without HeadXNet's input.

"We were interested in how these scans with AI-added overlays would improve the performance of clinicians," said Pranav Rajpurkar, a graduate student in computer science and co-lead author of the paper. "Rather than just having the algorithm say that a scan contained an aneurysm, we were able to bring the exact locations of the aneurysms to the clinician's attention."

Eight clinicians tested HeadXNet by evaluating a set of 115 brain scans for aneurysm, once with the help of HeadXNet and once without. With the tool, the clinicians correctly identified more aneurysms, and therefore reduced the "miss" rate, and the clinicians were more likely to agree with one another on what constituted an aneurysm. HeadXNet did not influence how long it took the clinicians to decide on a diagnosis or their ability to correctly identify scans without aneurysms — a guard against telling someone they have an aneurysm when they don't.

Other tasks and institutions

The machine learning methods at the heart of HeadXNet could likely be used to identify other diseases inside and outside the brain. For example, Yeom imagines a future version could focus on speeding up the identification of aneurysms after they have burst, saving precious time in an urgent situation. But a considerable hurdle remains in integrating any artificial intelligence medical tools with daily clinical workflow in radiology across hospitals.

Current scan viewers aren't designed to work with deep learning assistance, so the researchers had to custom-build tools to integrate HeadXNet within scan viewers. Similarly, variations in real-world data — as opposed to the data on which the algorithm is tested and trained — could reduce model performance. If the algorithm processes data from different kinds of scanners or imaging protocols, or a patient population that wasn't part of its original training, it might not work as expected.

"Because of these issues, I think deployment will come faster not with pure AI automation, but instead with AI and radiologists collaborating," Ng said. "We still have technical and nontechnical work to do, but we as a community will get there, and AI-radiologist collaboration is the most promising path."

L.A. CICERO/STANFORD NEWS SERVICE

HeadXNet team members (from left to right, Andrew Ng, Kristen Yeom, Christopher Chute, Pranav Rajpurkar and Allison Park) looking at a brain scan. Scans like this were used to train and test their artificial intelligence tool, which helps identify brain aneurysms.

Other Stanford co-authors are Joe Lou, undergraduate student in computer science; Robyn Ball, PhD, senior biostatistician at the Quantitative Sciences Unit; graduate students Katie Shpanskaya, Rashad Jabarkheel, Lily Kim and Emily McKenna; radiology residents Joe Tseng, MD, and Jason Ni, MD; Fidaa Wishah, MD, clinical instructor of radiology; Fred Wittber, MD, diagnostic radiology fellow; David Hong, MD, assistant professor of psychiatry and behavioral sciences; Thomas Wilson, MD, clinical assistant professor of neurosurgery; Safwan Halabi, MD, clinical associate professor of radiology; Sanjay Basu, MD, PhD, assistant professor of medicine; Bhavik Patel, MD, MBA, assistant professor of radiology; and Matthew Lungren, MD, MPH, assistant professor of radiology.

Hong and Yeom are also members of Stanford Bio-X, the Stanford Maternal and Child Health Research Institute and the Wu Tsai Neurosciences Institute at Stanford. Patel is also a member of Stanford Bio-X and the Stanford Cancer Institute. Lungren is a member of Stanford Bio-X, the Stanford Maternal and Child Health Research Institute and the Stanford Cancer Institute.

The work was supported by the National Center for Advancing Translational Science. Stanford's departments of Computer Science and of Radiology also supported the work. **ISM**

Annual awards honor outstanding teaching, patient care

AWARDS IN MEDICINE

Anna Caulfield, MD, clinical associate professor of neurology and neurological sciences; **Olivia Lee**, MD, clinical assistant professor of primary care and population health; and **Paul Mohabir**, MD, clinical professor of pulmonary and critical care medicine, received the Arthur L. Bloomfield Award in Recognition of Excellence in the Teaching of Clinical Medicine.

Lars Osterberg, MD, MPH, associate professor of primary care and population health, received the Franklin G. Ebaugh, Jr. Award for Excellence in Advising Medical Students.

Dean Winslow, MD, professor of medicine, received the Alwin C. Rambar-James BD Mark Award for Excellence in Patient Care, which recognizes a member of the medical faculty for compassion in working with patients and their families, excellence in providing medical treatment, and effectiveness and pleasantness in interactions with patient-care staff. He also received the Outstanding Lecture/Presentation Award.

Veronica Santini, MD, clinical associate professor of neurology and neurological sciences, received the Lawrence H. Mathers Award for Exceptional Commitment to Teaching and Active Involvement in Medical School Education.

Tracy Rydel, MD, clinical associate professor of primary care and population health, received the Award for Excellence in Promotion of the Learning Environment and Student Wellness.

Maria Alfonso, clerkship coordinator in emergency medicine, received the Medical Education Staff Service Award.

Peter Fay, MD, a physician at Santa Clara Valley Medical Center, received the Outstanding Community Clinic Preceptor, Preclinical Instruction Award.

Howard Chiou, visiting faculty member at the Clinical Excellence Research Center, received the Outstanding Community Clinical Preceptor, Clinical Instruction Award.

Rebecca Blankenburg, MD, MPH, clinical associate professor of pediatrics and of emergency medicine, received the Henry J. Kaiser Family Foundation Teaching Award for Outstanding and Innovative Contributions to Medical Education.

Ann Chuang, MD, adjunct clinical assistant professor of primary care and population health; **Pedram Fatehi**, MD, clinical associate professor of nephrology; and **Beth Martin-Kool**, MD, clinical assistant professor of hematology, received the Henry J. Kaiser Family Foundation Award for Excellence in Preclinical Teaching.

Aleah Brubaker, MD, PhD, resident in surgery; **Lucas Kipp**, MD, clinical assistant professor of neurology and neurological sciences; and **Tsuyoshi Mitarai**, MD, clinical associate professor of emergency medicine, received the Henry J. Kaiser Family Foundation Award for Excellence in Clinical Teaching.

Jessica Bentzley, Rishi Bhatnagar, Howard Chiou, Robert Tyler Payne, Surbhi Singhal and **Prateek Thatikunta** received the Arnold P. Gold Foundation Award for Humanism and Excellence in Teaching. The award is given to residents based on their commitment to teaching and the compassionate treatment of students, colleagues and patients and their families.

Michelle Drews, a medical student, received the Teaching Assistant Award.

Laural Braitman, PhD, adjunct professor of anesthesiology, perioperative and pain medicine; **Veronica Santini**, MD, clinical associate professor of neurology and neurological sciences; and **Erika Schillinger**, MD, clinical professor of primary care and population health, received the Award for Excellence in Promotion of Humanism.

Medical students **Sandrene Cassells** and **Richard Sapp** received the Award for Excellence in Promotion of Diversity and Societal Citizenship.

Medical students inducted into the Gold Humanism Honor Society include **Julie Barzilay, Sophia Bechek, Kathrine Casillas, Jeffrey Edwards, Daniel Greenberg, Michelle Han, Kristie Hsu, Elizabeth Hyde, Eli Johnson, Kevin Li, Palmoa Marin Nevarez, Jessica Pullen, Michael Richardson, Yekaterina Shpanskaya** and **Rosa Yu**. Members of the society, organized by the Arnold P. Gold Foundation, are selected for exemplifying compassionate patient care and serving as role models, mentors and leaders.

AWARDS IN BIOSCIENCE

David Schneider, PhD, professor and chair of microbiology and immunology, received the Award for Excellence in Graduate Teaching. This award recognizes faculty whose teaching of graduate students is distinguished and especially valued by School of Medicine and Biosciences faculty and graduate students.

Sheri Krams, PhD, professor of surgery, received the Award for Excellence in Diversity and Inclusion. This award recognizes faculty and academic staff who make distinguished contributions toward enhancing diversity, equity and inclusion across the Stanford Biosciences.

Dan Herschlag, PhD, professor of biochemistry, received the Award for Excellence in Mentoring and Service. This award recognizes faculty who make distinguished contributions toward enhancing the quality of training and the experiences of graduate students.

Graduate student **Amber Moore**, immunology, received the Student Award for Excellence in Societal Citizenship.

Graduate students **Michael Dubreuil**, cancer biology, and **Kendra Lechtenberg**, neurosciences, received the Student Award for Excellence in Teaching.

Graduate students **Lawrence Bai**, immunology; **Amy Fan**, immunology; **Julie Ko**, cancer biology; and **Makenna Morck**, biochemistry, received the Student Award for Excellence to Graduate Students. ISM

Graduation

continued from page 1

essential, but knowing how to adapt and embrace changes to your plan is just as crucial," he said.

Minor described his own "indirect journey," from finding the spark of his interest as an undergraduate, through 11 years of medical school and on to a successful scientific and clinical career. "I had arrived. I had accomplished the goal of my life's work," he said of the satisfaction he took in having his own lab and performing productive research that intersected with his clinical work and vice versa. "What I learned, though, was that I had only just arrived at another chapter.

"Remember," he added, "veering from the expected course is not a sign that you are lost. It means that you are a pathfinder. So, as you move forward in your careers, I encourage you to follow unmarked trails, explore unfamiliar territory and allow the pursuit of your passion to take you in new directions."

'Expression of the human soul'

Graduating speaker Brandon Turner, who received his medical degree with a concentration in informatics and data-driven medicine, reflected on the question of the right response to others' suffering, and suggested that physicians in particular must reengage with the world outside of health care.

"What's ironic is that for a profession devoted to serving others, we spend so much of it isolated in communities of like-minded individuals where everyone speaks this same language," Turner said. "Secluded, it can be easy to forget why we do this at all, and to rediscover that, I believe we must leave these places, we must look outside."

Graduating speaker Alejandro Schuler, who received his PhD in biomedical informatics, encouraged the audience to consider the value of science for its own sake, and that, to be truly revolutionary, we must let old ideas go.

"What I'm talking about is a science that has value beyond dollars and cents. We've spent years on these doctorates because we know that science is, like art, an expression of the human soul," Schuler said. "We need science for the same reason we need murals, ballet and film. If, as Carl Sagan said, we're a way for the universe to know itself, then science is nothing less than cosmic introspection."

Provost Persis Drell and Dean Lloyd Minor urged the graduates to anticipate changes in their future careers and to treat them as opportunities for growth.

STEVE FISCH

Nancy Nkansah-Mahaney was accompanied by her two children as she received her medical degree.

This year, 180 students walked across the stage — several with babies in arms or children by their side — to receive their diplomas. An additional 59 students met their graduation requirements over the course of the 2018-19 academic year. Of the 239 total students graduating, 88 earned MD degrees, 98 earned MS degrees and 69 PhDs, with 17 earning dual degrees such as MS/MD, MS/PhD or MD/PhD.

Nancy Nkansah-Mahaney celebrated with 17 members of her family and friends who traveled from Ghana, West Africa, Virginia, Florida, New York and Ohio. She walked the stage with her kids, Maya, 6, and Gavin, 5. After working for five years to earn her MD, she'll go on to a yearlong internship at Kaiser Permanente in Santa Clara, California, after which she'll head to Johns Hopkins for her residency in dermatology. And she'll carry on a project she started while at Stanford: an online platform to connect undergraduate students with mentors and professional training so that they can earn graduate degrees, too.

Brian Boursiquot was joined by his two younger brothers and parents, who flew in from New York and Los Angeles to see him graduate. For Boursiquot, who earned a master's degree in epidemiology along with his MD, commencement was a day to reconnect with his classmates before departing for a three-year internal medicine residency at New York-Presbyterian Hospital/Columbia University Medical Center. "Toward the end of med school, a lot of people end up having very different schedules," he said. "So it's really nice to be together with all your classmates again, and to see everyone before we all go off to residency. … It's been great, and it's just a culmination of all the hard work we put in." ISM

Two genes implicated in development of prostate enlargement

By Hanae Armitage

For aging men, prostate enlargement is almost as common as graying hair, and yet scientists know very little about why the prostate increases in size or how the process occurs on a molecular level.

In a new study, scientists at the School of Medicine have discovered a molecular pattern that flags prostate enlargement, also called benign prostatic hyperplasia, and have even identified two genes that likely play a role in the development of the condition.

The urethra runs directly through the prostate, a gland in the male reproductive system. And while a bigger prostate is not typically life-threatening in itself, it can cause urinary-related symptoms that range from niggling to severe. When the prostate becomes enlarged, it squeezes the urinary tube, causing problems such as incontinence or urinary urgency.

"It can be a terrible bother and, in the most severe cases, can even lead to kidney failure," said James Brooks, MD, professor of urology. Today's treatments work to an extent, but don't completely solve the issues, he added. "Urology as a field needs to do more to own this problem and figure out what the true underlying causes are so we can curb its prevalence and help treat it more effectively."

The new study is one of the first to describe a molecular landscape that differentiates enlarged prostate tissue from normal tissue. The team of scientists also discovered that the cell growth behind a ballooning prostate is not uniform. Several cell types comprise the prostate, and abnormal growth appears to come from an outburst of specific sets of cells, rather than an overall increase of all cell types.

A paper describing the study was published in the June 20 issue of *JCI Insight*. Brooks and professors of pathology Jonathan Pollack, MD, PhD, and Robert West, MD, PhD, share senior authorship. Former MD-PhD student Lance Middleton is the lead author.

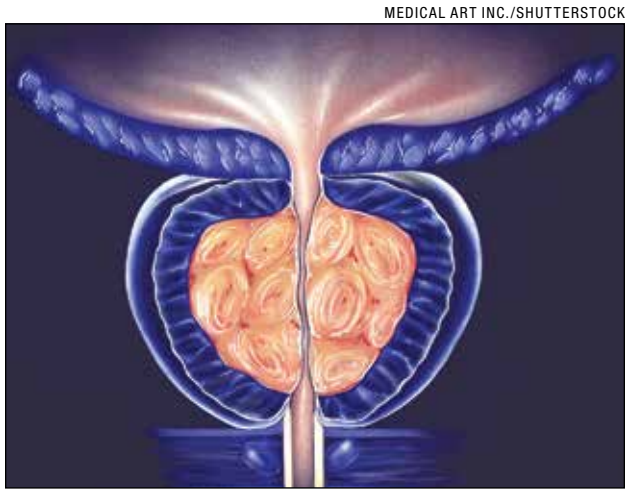
The plight of the prostate

No other gland in the human body, male or female, expands so predictably with age.

Fifty percent of men who are 50 years old have an enlarged prostate, and with every decade, that number increases by 10% (60% of men who are 60, 70% of men who are 70 and so on). A normal prostate is about the size of a walnut, but it can grow to twice that size, sometimes more.

"Researchers have hunted for mutations or growth factors that could trigger prostate growth, but there hasn't been much progress in finding a true cause," Brooks said.

MEDICAL ART INC./SHUTTERSTOCK



New research from Stanford indicates that only certain types of cells are responsible for enlargement of the prostate, a condition known as benign prostatic hyperplasia.

Brooks, Pollack and West took a multipronged approach in search of the answer, analyzing 49 tissue samples from patients who had their prostates removed. The odd thing about prostate enlargement, Brooks said, is that the entire prostate doesn't grow in unison; only certain parts of it expand. Some areas of the prostate actually remain unchanged.

Genomic analysis showed that most of the enlarged areas of the prostates consisted primarily of two types of cells — epithelial, which make up secretory glands, and stromal fibroblasts, which create structural parts of the prostate. That's not normal, Brooks said, and it clued the researchers into a new understanding of prostate growth: Only some cell types multiply in an enlarged prostate, taking over — and sometimes eliminating — other cell types, like weeds in a garden plot.

James Brooks

"So it's not just an increase in cells; it's a fundamental shift in the type of cells that make up the prostate. It's something we've termed 'cellular relandscaping,'" Pollack said. "It's possible that this shift is actually related to the disease progression, and not just arbitrary." One of the overrun cell types, Pollack said, is thought to be involved in the regulation of epithelial cell growth and development.

Beyond cell type, the researchers analyzed the molecular state of normal and enlarged prostate tissues, looking at data that showed which genes were active in enlarged prostate samples and which were active in normal samples. By comparing gene activity, they found 65 genes whose expression patterns strongly correlated with prostate enlargement. In other words, tissue samples of enlarged prostates reliably showed this gene signature, whereas healthy samples did not. What's more, patients whose prostate tissues strongly correlated with this gene signature reported more severe symptoms.

Two genetic suspects

While the overall signature is only correlation at this point, Brooks and Pollack have singled out two genes involved in cell signaling that they suspect may play a role in the condition's development. One, CXCL13, codes for a protein involved in immune cell recruitment, which Pollack said makes sense because prostate enlargement involves inflammation. The other gene, BMP5, codes for a molecule involved in cell identity and development. Whereas CXCL13 effects are complicated to model in the lab, it's relatively easy to manipulate BMP5. So the researchers rigged an experiment to test if adding a BMP5-laden concoction could change the characteristics of normal prostate tissue. They found that healthy prostate samples could be coerced into expressing the 65-gene signature seen in enlarged prostates.

"They even start to proliferate a little bit," Brooks said. "It's quite remarkable that with this one molecule, we can turn healthy samples into samples that mirror the molecular landscape of an enlarged prostate."

It's still early in the research, the scientists said, and more work needs to be done to confirm the role of BMP5 and CXCL13. But it's a promising step toward finding new avenues for drug development.

Other Stanford co-authors of the study are former postdoctoral scholars Zhewei Shen, PhD, and Okyaz Eminaga, PhD; research assistants Sushama Varma, Jewison Biscocho and Rosalie Nolley; research scientists Anna Pollack, MD, Shirley Zhu, Chunfang Zhu, PhD, and Joseph Foley, PhD; former research scientist Xue Gong, PhD; research associates Sujay Vennam and Robert Sweeney, MD; and professor of biomedical data science and of statistics Robert Tibshirani, PhD.

This study was supported by the National Institutes of Health. ISM

Stanford Medicine magazine brings joy of discovery into focus

By Patricia Hannon

It's strange. It's surprising. It's fascinating. It can also be tedious and infuriating.

But talk to people who spend their careers uncovering the mysteries of life through the lens of a microscope, and they'll likely say there isn't anything they'd rather do. That's because, even as their work is rife with opportunity for failure, one thing isn't in question: Fundamental research is really cool.

In the latest issue of *Stanford Medicine*, you'll meet current and future scientists with a passion for research and discovery. You'll see what's possible when their discoveries translate into cures for some of our most devastating diseases. You'll also learn that some are as passionate about instilling a love of science in future generations as they are about research itself.

One story looks at how the MD program was overhauled to encourage more medical students to pursue research. In the article, Lloyd Minor, MD, dean of the School of Medicine, describes the students, faculty and Nobel laureates who developed the curriculum as "true innovators in medical education."

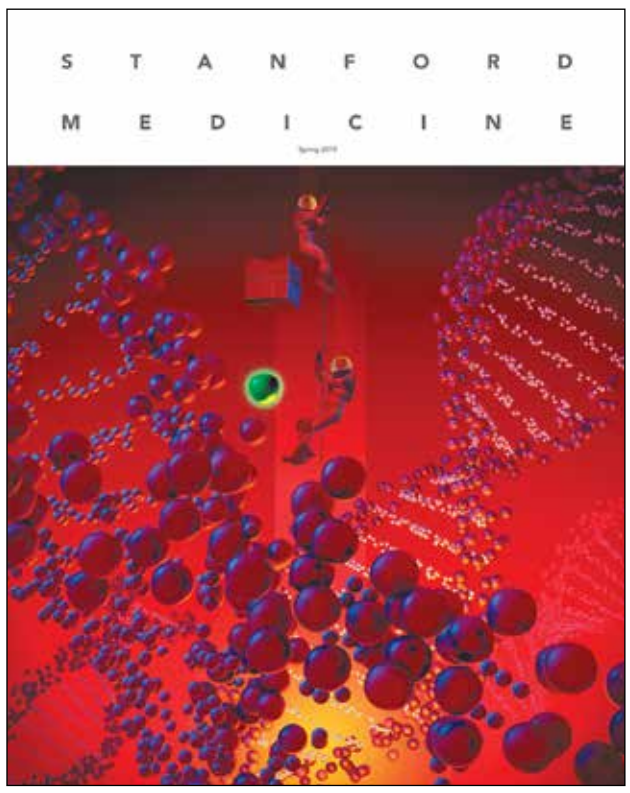
"Their efforts will facilitate pursuits of fundamental discovery that further our precision health vision, provide our students with a more flexible and distinctive learning experience, and expedite the preparation of physician-scientists to become leaders in biomedical investigation," Minor said.

Many of the stories in this issue show how the thrill of discovery is being realized at Stanford Medicine and beyond:

- A roundup of basic biology research puts tiny organelles, tadpole tails and flesh-ravaging parasites at center stage to illustrate how some of the curiosity-driven biology under investigation at Stanford is fueling the future of medical discovery.
- The team members in the neuroscience lab of Miriam Goodman, PhD, are studying tiny worms to better understand our sense of touch, but the plans and dreams that brought them into science in the first place are likely to lead them in new directions.
- Brianna Rivera was nervous and a bit intimidated when she entered FAST, a high school biology program run by Stanford graduate students who act as mentors and aim to spark a passion for science in their disciples. Soon, Rivera became known on her high school campus as "the girl who loves science." She's now a college freshman studying biomedical engineering. A video about her and the program accompanies the story online.
- National Institutes of Health director Francis Collins, MD, still loves to slip into his lab to catch up on research there. "The opportunity to not just oversee what's happening in the research community, but also to participate, at least in a small way, drives me to get up in the morning," he said in a Q&A with podcast host Paul Costello.
- Two neurosurgical residents traded in their scrubs for lab coats so they could research how deadly brain tumors in children develop and try to find an effective treatment. They ended up joining the Stanford lab of developmental biologist Matthew Scott, PhD, and identified a potential new drug therapy that is now in a clinical trial.
- When Provenge, a drug developed out of the Stanford lab of Edgar Engleman, MD, was approved by the Food and Drug Administration in 2010 as the first immunotherapy cancer drug for use in patients, it helped set the stage for a revolution in cancer treatment. But the path to wide acceptance for the concept was a rough one. Now the drug is undergoing new testing and analysis.

Also in this issue, in an excerpt from her book *The Unspeakable Mind*, Stanford psychiatrist Shaili Jain, MD, shares what she's learned about the legacy of trauma in our lives, and about how to treat people with PTSD. And two young brothers beat the odds and are able to undergo successful stem cell transplants to halt the symptoms of a rare genetic disease called IPEX syndrome.

Print copies of the magazine are being sent to subscribers. Others can request a copy at (650) 723-6911 or by sending an email to medmag@stanford.edu. ISM



5 QUESTIONS

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

Aiding the fight against antibiotic resistance

The discovery of antibiotics like penicillin in the late 1920s revolutionized medicine, making surgeries safer and common bacterial infections less deadly. But the overuse and misuse of these lifesaving drugs has evolved into a global public health emergency: Many microorganisms naturally develop resistance to antibiotics over time, allowing for the emergence of "superbugs" that are no longer readily killed by available antibiotics.

After several years of working with the World Health Organization to promote the safe and optimal use of antibiotics worldwide, the Stanford Antimicrobial Safety and Sustainability program has been designated a WHO Collaborating Centre for Antimicrobial Resistance and Stewardship — the first designation of its kind.

Leading this effort are Stanford physician-scientists Stanley Deresinski, MD, clinical professor of infectious diseases, and Marisa Holubar, MD, clinical assistant professor of infectious diseases. Writer Julie Greicius reached out to them to learn more about the issue and Stanford's role in optimizing the use of antibiotics.

1 What makes antimicrobial resistance a global public health emergency?

DERESINSKI: Antibiotics are unlike other classes of drugs in that their very use guarantees their eventual obsolescence. As antibiotics lose their effectiveness, the treatment of infections becomes increasingly difficult and, in some cases, totally ineffective. As a consequence, there is concern that we are heading toward a post-antibiotic era — effectively reverting to a time before the availability of these "wonder drugs." Without antibiotics, even a minor surgery could become life-threatening if ordinary antibiotics can't control infection. Recent predictions forecast that antimicrobial resistant infections could cause 10 million deaths globally each year by 2050. This demands immediate and coordinated action to avert disaster.

2 What does it mean to be a World Health Organization Collaborating Centre, and what will be Stanford's role specifically?

HOLUBAR: WHO Collaborating Centre designations recognize at least two years of productive collaboration between the institution and WHO, and continued excellence in the field. Specifically, we will provide technical support and guidance to the WHO to strengthen the capacity of nations to implement antimicrobial stewardship programs in clinical care. We will also continue to develop and refine educational curricula and programs designed to enhance the competency of antimicrobial prescribers.

3 What led to your collaboration with the WHO?

Stanley Deresinski

Marisa Holubar

DERESINSKI: After starting our program at Stanford in 2012, we developed a massive open online course, Antimicrobial Stewardship: Improving Clinical Outcomes by Optimization of Antibiotic Practices, in which more than 30,000 students have enrolled. At the time, our colleagues at WHO in Copenhagen were looking for such freely available educational material and contacted us. We have been working with them ever since. Most recently, we developed a web-based course for WHO, titled Antimicrobial Stewardship: A Competency Based Approach, which has enrolled over 21,000 since its release in January 2018. Other activities have included developing and implementing antimicrobial stewardship curricula, and participating in WHO missions in places such as Turkey, Armenia, Jordan and Uzbekistan.

4 What are the next steps in this collaboration?

HOLUBAR: Optimizing the use of antimicrobials in resource-limited settings is complex and activities must be tailored to available resources. The complexity is illustrated by the fact that antibiotic overuse exists side by side with lack of access in some lower-income countries. There is no one-size-fits-all solution. For example, American stewardship programs typically are led by infectious disease physicians and pharmacists, but health care workers with this kind of training are uncommon in some countries. We are interested in developing resources, including educational materials, to help member states get started with their available resources and formally assess their progress.

5 What are the most important steps that physicians and patients can take to begin reducing antimicrobial resistance?

DERESINSKI: Clinicians should never consider antibiotic prescribing as routine. They should always take into account the balance between possible benefit and harm — not only to the individual patient, but to subsequent patients because of the effect of antibiotics on the microbiome and on the emergence of resistance.

Patients can learn the difference in symptoms between common viral infections, for which antibiotics provide no benefit, and more serious problems that may be due to bacterial infection. They should understand that antibiotics, although necessary in some circumstances, can also have harmful effects. **ISM**

Fire

continued from page 1

"Fire departments are receiving hands-on training from Stanford physicians in advanced emergency medical services, and fire personnel can turn around and provide very high-level care to the populations they are serving," Gautreau said. "We've seen several great saves as a result of the advanced resuscitation skills implemented by local fire department paramedics. And we can provide training during shift hours, which means stations don't need to pay overtime for training, and resources can be directed toward offering the best care possible."

A chance encounter

The idea for the partnership arose in 2016 when Kim Roderick, chief of emergency medical services for the Palo Alto Fire Department, stopped by the Stanford Hospital coffee cart. Roderick happened to see D'Souza, who had been involved with the fire department for many years and had collaborated with Roderick on a study in which first responders were taught a new method of delivering an anti-seizure medication.

As the two chatted, Roderick asked D'Souza if he was interested in becoming the medical adviser for a number of fire departments in Santa Clara County, but D'Souza and his wife were expecting their first child and he felt the timing wasn't right to take on additional work. However, D'Souza proposed an alternative: The collective resources at Stanford Emergency Medicine could provide medical support for Palo Alto and other Santa Clara County fire agencies.

The idea of having an institution take on the role of medical director was untested, so there were no road maps to follow. "We brainstormed about using the entire physician group, and it kind of went from there," Roderick said. D'Souza discussed the possibility with Stanford Emergency Medicine leaders, and Roderick shared the idea with fire chiefs in the area. Two months later, they pitched the idea to 10 emergency medical services chiefs in Santa Clara County. "They loved it," Roderick said.

After a formal proposal process, Stanford took on the role for the Palo Alto Fire Department on Jan. 1, 2017. Stanford signed agreements with eight more fire agencies in the ensuing months.

RAFAEL CRUZ

D'Souza and his Stanford colleagues provide training in the latest emergency techniques to firefighter-paramedics in nine Santa Clara County fire agencies.

In one of the initial training sessions, Stanford faculty instructed Palo Alto firefighters on high-performance CPR, which optimizes resuscitation during cardiac arrest. HP-CPR requires a team of trained individuals who rotate through different roles to minimize the downtime between chest compressions. The goal of HP-CPR is not simply to save the patient, but to minimize the loss of brain function, enabling patients to resume their lives with minimal lasting damage.

The Palo Alto Fire Department immediately implemented the techniques, with positive results. "We used to see a return of spontaneous circulation in 17% of the patients," Roderick said, meaning that those patients were able to breathe and their hearts resumed pumping blood. "With HP-CPR we see spontaneous circulation in 20% to 25% of patients."

This was not an isolated result. Stanford recently trained members of the Santa Clara Fire Department in using a video laryngoscope, which enables responders to quickly insert a breathing tube without stopping chest compressions. One week later, D'Souza received a text message from the department's emergency medical services chief noting that crews had successfully used the approach on three separate emergency calls.

Finding out how the patients fared

Another benefit of the partnership is the ability to close the loop about critical patients or challenging emergency medical treatments. Roderick said 97% of the people the firefighter-paramedics transport end up at Stanford Hospital. But in her three decades on the job, she rarely learned the outcomes of the cases once they passed through the hospital doors. "We didn't really know if we were having an impact," she said. "Most health care providers review cases and assess actions on a regular basis, but we didn't have that opportunity. Now, we can share lessons learned. We can reinforce techniques that have the best result."

The partnership has also given the fire departments access to experts including the four Stanford faculty members who are board certified in emergency medical services — only 600 or so are certified in the country, so they are a rarity in fire departments. In addition, clinical assistant professor of emergency medicine Justin Lemieux, MD, who has had extensive training in combat casualty and tactical emergency operations, can provide training for a hostile situation such as a mass shooting.

The partnership with Stanford is also helping fire departments prepare for a new "community paramedicine" model that would enable first responders to undergo training on a wider range of treatments, possibly saving patients a trip to the emergency department. For example, the first responders could treat a bad asthma attack onsite. The state of California is developing a scope of practice that could enable paramedics to treat conditions that are now commonly handled in emergency departments. Having fire departments participate in the model makes sense, Roderick said. "Why not include options for the patients besides transports to an ER? Patients might prefer more options depending on the emergency," she said.

Stanford recently acquired an emergency response vehicle that is being retrofitted to serve as a mobile training unit. Between scheduled trainings, physicians will be able to travel to stations to provide short refresher courses to firefighters while they are on shift. D'Souza and Roderick also hope to incorporate timely, case-specific simulations in response to unusual medical scenarios that firefighters encounter.

"We want to ensure our patients have the best odds of survival, even before they set foot in the emergency department," D'Souza said. "Our commitment is to serve our community and provide the best possible care at every stage. In order to do so, we have to reach beyond the walls of the hospital." **ISM**

Antibody treatment allows mismatched stem cell transplants

By Krista Conger

A combination of six antibodies can successfully prepare mice to accept blood and immune stem cells from an immunologically mismatched donor, according to a study by researchers at the School of Medicine.

The recipient animals can then accept an organ or tissue transplant matching that of the donor stem cells without requiring ongoing immune suppression.

If the findings are replicated in humans, the work could transform the treatment of people with immune or blood disorders while also vastly increasing the pool of available organs for those who need transplants.

The work builds on a series of recent studies conducted at Stanford that may pave the way for this type of stem cell transplant, known as a hematopoietic stem cell transplant, to safely treat a variety of disorders. The technique is now primarily used to treat cancers of the blood and immune system.

"Radiation and chemotherapy are the current standard for preparing patients for a bone marrow transplant," said Irving Weissman, MD, professor of pathology and developmental biology at Stanford. "For the past decade, we have been working to step-by-step replace these nonselective and dangerous treatments with targeted antibodies. This study is an important milestone that began with our isolation of purified blood stem cells 30 years ago."

Weissman, the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine and of the Ludwig Center for Cancer Stem Cell Research and Medicine at Stanford, is the senior author of the study, which was published online June 13 in *Cell Stem Cell*. Graduate student Benson George is the lead author.

"This study indicates that it's possible to perform these transplants in mice in a much gentler way without requiring a complete match between the donor and the recipient stem cells," George said. "It also opens the door to increasing the availability of solid organs for transplant."

Harsh process

Hematopoietic stem cells are a rare type of stem cell in the bone marrow that give rise to the progenitors of all blood and immune cells throughout our lives. It's been known for some time that people with genetic blood disorders such as sickle cell anemia or thalassemia, or those with autoimmune diseases or immune deficiencies, can be cured by a transplant of healthy hematopoietic stem cells. But in order for the transplanted cells to settle in to the recipient's bone marrow — a process known as engrafting — it's first necessary to eliminate key components of the recipient's own blood and immune system.

Traditionally this has been accomplished with toxic doses of chemotherapy or radiation, or both. But this pretreatment, known as conditioning, is so harsh that clinicians have been hesitant to resort to hematopoietic stem cell transplantation unless the patient's life is threatened by their disease. For this reason, most transplant recipients have been people with cancers such as leukemia or lymphoma.

Hematopoietic stem cells for transplant are typically obtained by collecting them from either circulating blood (although the cells usually live in the bone marrow they can be induced by specific drugs to enter the blood) or from the bone marrow itself, which is why the procedure is often referred to as a bone marrow transplant. In either case, the recipient receives a mixture of cells from the donor, only some of which are hematopoietic stem cells.

Unfortunately, some of those passenger cells include a type of immune cell called a T cell, which Weissman and others have shown is responsible for a life-threatening transplant complication called graft-versus-host disease. This occurs when the donor's cells recognize the recipient's tissues as foreign and begin to attack it. Clinicians try to reduce the likelihood of graft-versus-host disease by using donor stem cells that immunologically match the recipient as closely as possible. But those matches can be difficult to find, particularly for some ethnic minorities. Although it's possible to do transplants with less-than-perfect matches — a situation known as a haploidentical transplant — the recipient then requires ongoing treatment with strong immunosuppressive drugs to prevent rejection or graft-versus-host disease.

Although pure hematopoietic stem cell transplants avoid this outcome, they are more difficult to obtain in sufficient quantities, and they engraft less readily than whole bone marrow.

"We wanted to eliminate three major barriers: the toxicity of the conditioning procedure, the need to have an immunologically matched donor and the difficulties in transplanting purified hematopoietic stem cells," George said.

Hopes for first-line therapy

The researchers found that treating mice with a combination of six specific antibodies safely and efficiently eliminated several types of immune cells in the animals' bone marrow and allowed haploidentical pure hematopoietic stem cells to engraft and begin producing blood and immune cells without the need for continued immunosuppression.

The degree of difference in a haploidentical transplant is similar to what naturally occurs between parent and child, or between about half of siblings.

"This finding suggests that, if these results are replicated in humans, we could have a child with sickle cell anemia in the clinic and, rather than considering stem cell transplant as a last resort and contingent on finding a perfectly matching donor, we could instead turn to transplant with stem cells from one of the child's parents as a first-line therapy," George said.

Additional experiments showed that the mice treated with the six antibodies could also accept completely mismatched purified hematopoietic stem cells, such as those that might be obtained from an embryonic stem cell line.

After transplantation with the mismatched stem cells, the recipient mice developed blood and immune systems that contained cells from both the donor and the recipient. This allowed them to subsequently accept transplants of heart tissue from animals genetically identical to the donor animals.

"The immune systems exist together in a kind of a symbiosis," George said, "and they view both the donor and recipient tissue as 'self.' This suggests that it may be possible to make haploidentical stem transplants both safe and achievable in human patients without the need for either conditioning with radiation or chemotherapy or subsequent immunosuppression."

NORBERT VON DER GROEBEN

Irving Weissman and his collaborators have found a way to prepare mice for a transplant of blood and immune cells, even when a donor and recipient are immunologically mismatched.

The researchers are next planning to conduct similar antibody-mediated conditioning followed by transplant with mismatched hematopoietic stem cells in large animal models.

If the technique one day clears the hurdles necessary to prove it is safe and effective in humans, the researchers envision a time when people who need transplanted organs could first undergo a safe, gentle transplant with hematopoietic stem cells derived in the laboratory from embryonic stem cells. The same embryonic stem cells could also then be used to generate an organ that would be fully accepted by the recipient without requiring the need for long-term treatment with drugs to suppress the immune system. In particular, Hiromitsu Nakauchi, MD, PhD, a professor of genetics at Stanford, is studying how to generate human organs in large animals from laboratory-grown stem cells.

Other Stanford co-authors of the study are technician Kevin Kao; research associate Hye-Sook Kwon, PhD; graduate students Brenda Velasco and Malachia Hoover; life science researchers Jessica Poyser and Alan Le; research assistant Angela Chen; postdoctoral scholar Akanksha Chhabra, PhD; former research assistant Cassandra Burnett; former research associate Devon Cajuste; assistant professor of developmental biology Kyle Loh, PhD; and professor of medicine Judith Shizuru, MD, PhD.

The study was supported by the National Institutes of Health, the California Institute for Regenerative Medicine, the Ludwig Cancer Foundation, the Stanford-UC Berkeley Siebel Stem Cell Institute, the Stanford Beckman Center, the Baxter Foundation, an anonymous family and the DiGenova family. ISM

Marijuana

continued from page 1

of medical cannabis, said Keith Humphreys, PhD, professor of psychiatry and behavioral sciences.

"If you think opening a bunch of dispensaries is going to reduce opioid deaths, you'll be disappointed," Humphreys said. "We don't think cannabis is killing people, but we don't think it's saving people."

A paper describing the new study was published online June 10 in *Proceedings of the National Academy of Sciences*. Humphreys is the senior author. The lead author is postdoctoral scholar Chelsea Shover, PhD.

Medical pot now legal in 47 states

In 1996, California became the first state to legalize medical marijuana. By 2010, 13 states, most of them in the West, had legalized medical marijuana. Today, 47 states permit some version of medical pot.

For the new study, the Stanford researchers used the same method employed in the 2014 study to evaluate the connection between legalized medical marijuana and fatal opioid overdoses. They confirmed the findings from the 2014 study, but when they looked at opioid deaths up to 2017 — by which point most states had legalized some form of medical marijuana, if not recreational marijuana — they found that the opposite was true: States with legal medical marijuana had a higher rate of deaths due to opioid overdose.

Keith Humphreys

After the 2014 study was released, medical marijuana proponents and some public officials interpreted the results to mean that, given access to legalized pot, people would turn to it rather than opioids for pain relief or recreation.

Yet when the Stanford researchers compared states that have more restrictive medical marijuana laws with those that allow recreational marijuana, they found no correlation between opioid overdose mortality and the level of restriction.

"Accounting for different types of laws didn't change the bottom line," Shover said.

Also, given that only 2.5% of the U.S. population uses medical marijuana, it's unlikely that use could affect mortality statistics, the researchers said.

'Something else about those states'

Humphreys said the results of the 2014 study may have reflected policies and conditions in states that legalized medical marijuana early. Those states tended to be wealthier and more politically liberal, with greater access to addiction treatment and to naloxone, which reverses the effects of opioids and can prevent overdose fatalities.

The states that legalized pot early also incarcerate fewer people for drug use, Humphreys added. When people are released from prison, where they lack access to drugs and lose tolerance to them, they may try to use the same levels as they did before they were incarcerated, leading to overdose.

The finding of lower death rates "wasn't about the cannabis," Humphreys said. "It was something else about those states."

Humphreys and Shover said they believe that medical marijuana provides benefits and that research into its effectiveness should continue.

"There are valid reasons to pursue medical cannabis policies, but this doesn't seem to be one of them," Shover said. "I urge researchers and policymakers to focus on other ways to reduce mortality due to opioid overdoses."

Humphreys is a member of the Wu Tsai Neurosciences Institute at Stanford, the Stanford Center for Innovation in Global Health and the Stanford Center for Health Policy.

Researchers at the Network for Public Health Law and New York University also contributed to the study.

The research was funded by the National Institutes of Health and the U.S. Department of Veterans Affairs. ISM

Stanford hospitals get reverification as Level I trauma center

By Kate DeTrempe

Stanford Health Care and Lucile Packard Children's Hospital Stanford have been reverified as a Level I adult and pediatric trauma center through May 2022 by the American College of Surgeons.

Level I verification is the highest possible ranking for trauma centers and recognizes the hospitals' dedication to providing the best possible care for all injured patients.

Stanford Health Care/Lucile Packard Children's Hospital Stanford is one of only five American College of Surgeons-verified Level I pediatric trauma centers in California, and receives pediatric trauma patients from as far north as the Oregon border and as far south as Bakersfield. It is the only Level I pediatric trauma center on the San Francisco Peninsula. Stanford Health Care has been recognized as a Level I trauma center for more than 20 years.

Verified hospitals must provide a full spectrum of care to address the needs of all injured patients and must provide access to the following:

- Coordinated, timely response from all necessary specialty medical staff.
- 24-hour availability of trauma surgeons and emergency medicine doctors, including pediatric surgeons.
- Operating rooms that are equipped and ready at all times.
- Neurosurgical and neurological care for severely injured patients.
- Orthopaedic care for severely injured patients.
- A pediatric intensive care unit for the special needs of children with serious illnesses or injuries.
- In-hospital anesthesiologists.

"Stanford is proud to be recognized as the singular and most comprehensive Level I adult and Level I pediatric trauma resource on the Peninsula," said David Spain, MD, chief of trauma and critical care surgery at Stanford Health Care and professor of surgery at the Stanford School of Medicine. "The many departments and caregivers within Stanford Health Care and Lucile Packard Children's Hospital Stanford have worked closely to seamlessly address the needs of all our patients. The ACS reverification reflects our ongoing commitment to leading-edge, patient-centered care."

Collectively, the two hospitals see approximately 2,870 trauma patients per year, with 63% of those patients requiring hospital admission — the most admissions of any trauma center in Santa Clara County.

PACKARD CHILDREN'S HOSPITAL

Stanford's hospitals serve as a Level I trauma center, meaning that they have a full range of services to meet patients' needs.

"Lucile Packard Children's Hospital Stanford provides unparalleled specialty care, which allows us to quickly and safely deliver the best possible treatment for traumatically injured children," said Stephanie Chao, MD, pediatric trauma medical director at Stanford Children's Health and assistant professor of pediatric surgery at the School of Medicine.

The ACS is a scientific and educational association of surgeons founded in 1913 to raise the standards of surgical education and practice and to improve the care of surgical patients. **ISM**

Alumni association honors 6 medical students for community leadership

Six students at the School of Medicine are among the 35 winners of the 2019 Community Impact Award from the Stanford Alumni Association.

The award recognizes students who have enhanced the Stanford community through exemplary leadership, creation of an event or program, or other significant campus contribution.

Students were nominated by Stanford faculty, staff and senior administrators.

The recipients in the School of Medicine are:

MELODYANNE CHENG, a student in the master of laboratory animal science program, who was recognized for her efforts as a proactive community-builder for current and prospective students and alumni of the program; for her public health advocacy work in low-income and migrant communities; and for her leadership in Dancebreak, a weekly social dance event that provides a creative outlet for the graduate student community.

AMY FAN, a graduate student in immunology, who was recognized for her leadership in the Biomedical Association for the Interest of Minority Students and dedication to supporting fellow students of color and affinity groups through mentorship, and her efforts to bring together individuals and groups who share a common mission.

TIMOTHY KEYES, a medical student and graduate student in cancer biology, who was recognized for leading the school's health equity, diversity and inclusion activities; serving as co-chair of the Stanford Minority Medical Alliance; organizing the dean's first town hall on LGBTQ+ affairs; and helping to develop Stanford Medicine's first LGBTQ+ forum to celebrate visibility.

JESSICA RIBADO, a graduate student in genetics, who was awarded for leadership of the Stanford Science Policy Group and the Stanford Summer Research program, and for the creation of an outreach program for local middle schoolers.

ROSA YU, a medical student, who was recognized for contributing to the creation of the School of Medicine's Diversity Center for Representation and Equity, which aims to strengthen support and understanding of issues faced by students from traditionally marginalized groups; planning programming to address the mental health of medical students and graduate students; and mentoring first-generation, low-income students interested in the fields of science, technology, engineering and mathematics.

BRIGHT ZHOU, a medical student, who was recognized for leadership in the Asian Pacific American Medical Students Association; efforts to highlight disparities in health care for Asian American and LGBTQ+ patients; and outreach to the Asian American and LGBTQ+ communities through free-clinic and community center interventions. **ISM**

OF NOTE

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

MARK BERRY, MD, was promoted to professor of cardiothoracic surgery, effective March 1. He specializes in treating thoracic surgical conditions with minimally invasive techniques, such as video-assisted thoracoscopic surgery and laparoscopic, robotic, endoscopic and bronchoscopic approaches. His research focuses on the use of such techniques and on evaluating outcomes after treatment of thoracic malignancies.

MIMI BORELLI, MBBS, a postdoctoral scholar in plastic and reconstructive surgery, was awarded a pilot research grant from The Plastic Surgery Foundation. The $10,000 award will fund her research on the cJUN protein and how it regulates a profibrotic wound healing response.

DOMINIC HENN, MD, postdoctoral research fellow in plastic and reconstructive surgery, received a translational research grant from The Plastic Surgery Foundation. The $50,000 grant will support his research exploring the application of CRISPR/Cas9-edited dendritic cells for angiogenesis and wound healing.

KYLE LOH, PhD, assistant professor of developmental biology, has been named a Pew Scholar in the Biomedical Sciences. The program provides funding to young investigators of outstanding promise. He will receive $300,000 over four years to support his research focused on embryonic stem cell differentiation and tissue transplants.

MICHAEL LONGAKER, MD, the Deane P. and Louise Mitchell Professor in the School of Medicine and co-director of the Institute for Stem Cell Biology and Regenerative Medicine, was awarded the Lifetime Achievement award by the Society of University Surgeons. The award recognizes individuals with careers in academic surgery who have made contributions to surgical science, and demonstrated a commitment to the society.

MICHAEL OSTACHER, MD, MPH, was promoted to professor of psychiatry and behavioral sciences, effective March 1. He directs the Bipolar Disorder and Depression Research Program at the Veterans Affairs Palo Alto Health Care System. His primary research interest is in large clinical trials in bipolar disorder and depression, and the implementation of evidence-based mental health practices.

JORDAN TAYLOR, MD, research fellow in pediatric surgery, received the Quick Shots of Distinction Award in Basic Science from the American Pediatric Surgical Association. The award recognized his research on lengthening the small intestine by placing a compressed spring within the bowel.

LU TIAN, ScD, was promoted to professor of biomedical data science, effective March 1. His research focuses on developing advanced statistical methods for predicting health outcomes and guiding the practice of precision medicine. He is also interested in statistical methodology to integrate information from multiple sources, including data from clinical trials and patient outcomes.

XINNAN WANG, MD, PhD, was promoted to associate professor of neurosurgery, effective April 1. Her research focuses on investigating the mechanisms controlling the transport and function of mitochondria, with an emphasis on understanding how even subtle interference with these processes may contribute to neurodegenerative disorders.

JOANNA WYSOCKA, PhD, the Lorry Lokey Professor and professor of chemical and systems biology and of developmental biology, was elected as an associate member of the European Molecular Biology Organization, a group of researchers who promote excellence in the life sciences in Europe and beyond. **ISM**

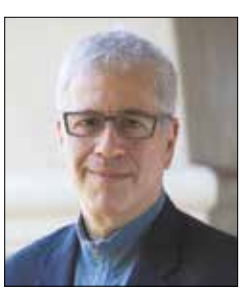
Mark Berry

Mimi Borelli

Dominic Henn

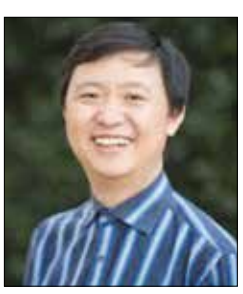
Kyle Loh

Michael Longaker



Michael Ostacher

Jordan Taylor



Lu Tian

Xinnan Wang

Joanna Wysocka