INSIDE STANFORD MEDICINE

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Pursuing parity in academic medicine, female faculty members are gathering data on why there should be more of them.

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Hallucinogen investigated as OCD treatment

By Tracie White

The first time psychiatrist Carolyn Rodriguez gave an infusion of ketamine to a patient with obsessive-compulsive disorder, she was nervous. After all, while ketamine is approved by the Federal Drug Administration as an anesthetic, it is also an illicit party drug known as "Special K," with hallucinogenic effects and the potential for abuse.

"As a physician, you take an oath to do no harm," said Rodriguez, MD, PhD, an assistant professor of psychiatry and behavioral sciences at the School of Medicine. "There are caveats with ketamine. People can feel disassociated, like they are floating; some feel nauseated."

But the results simply astonished her.

The patient was a 24-year-old woman who had for years spent eight hours a day checking and rechecking that objects were precisely in place, due to her obsessions with symmetry and exactness. Midway through the 40-minute ketamine infusion, the patient said all obsessive thoughts and urges had suddenly disappeared.

"She was a lovely student who was very debilitated by her OCD," said Rodriguez, who was an assistant professor at Columbia University at the time of this study of an individual patient, in 2009. "When I gave her the infusion, she was describing what she was feeling. About 20 minutes into the infusion, she just looked at me, eyes wide open, and said, 'I feel like this weight has been lifted. Like I'm having a vacation from my OCD.'

Fresh hope

"It was a very surreal moment. I thought, 'Is she really saying that?' I remember my heart was racing. I went back to my lab and said, 'You will not believe this: It works.'"

Ketamine has brought fresh hope to a field desperate to find new treatments for hard-to-treat disorders such as severe OCD, a chronic condition marked by debilitating obsessions and repetitive behaviors. Current treatments, which include antidepressants such as Prozac, can take months to have any effect on the disease, if they work at all.

"Severe OCD takes such a toll on patients," Rodriguez said. "The constant, intrusive thoughts that something is contaminated, the checking and rechecking, the repetitive behaviors. It interferes with your life, your jobs, your relationships."

Over the past 10 years, dozens of small studies have reported remarkable results in the use of ketamine to treat a variety of mood and anxiety disorders. Findings include the sudden alleviation of treatment-resistant depression, bipolar disorder and post-traumatic stress disorder. And these effects lasted days, sometimes weeks, after the hallucinogenic effects of the drug wore off.

Ketamine was developed in the 1960s and has been used for decades as an anesthetic during surgery. It can cause dissociative side effects — hallucinations and other psychotic-like symptoms — and has been used as a recreational drug. If used regularly, it can lead to dependence. It remains a mystery just how the drug works in the brain, and there are safety concerns about its current off-label use to treat patients (*see sidebar, page 6*). But researchers like Rodriguez are intrigued about the drug's potential to help them identify a whole new line of medicines for fast-acting treatment of mental health disorders.

"What most excites me about ketamine is that it works in a different way than traditional antidepressants," Rodriguez said. "Using ketamine, we hope to understand the neurobiology that could lead to safe, fast-acting treatments. I feel that is part of my See KETAMINE, page 6

PAUL SAKUMA

Carolyn Rodriguez is studying the effects of ketamine on the brains of patients with obsessive-compulsive disorder, hoping to determine why, in studies, the drug has provided relief from symptoms.

Cancer therapy activates macrophages, prompting scientists to rethink how it works

By Christopher Vaughan

Antibodies to the proteins PD-1 and PD-L1 have been shown to fight cancer by unleashing the body's T cells, a type of immune cell. Now, researchers at the School of Medicine have shown that the therapy also fights cancer in a completely different way, by prompting immune cells called macrophages to engulf and devour cancer cells.

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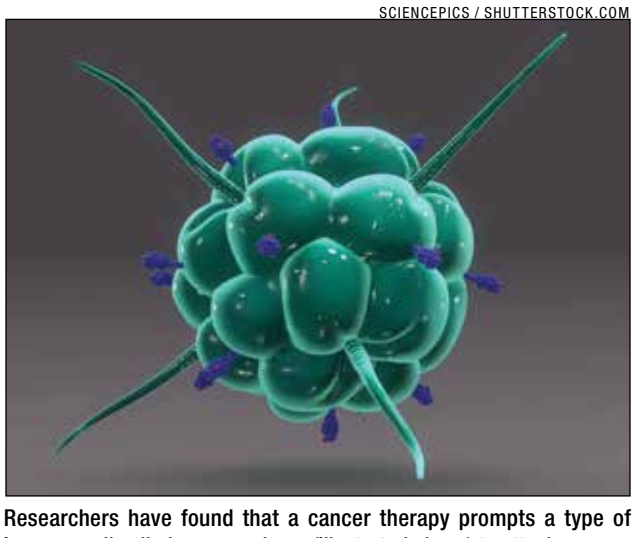

Researchers have found that a cancer therapy prompts a type of immune cell called a macrophage (illustrated above) to attack cancer.

The finding may have important implications for improving and expanding the use of this cancer treatment, the researchers said.

A study describing the work, which was done in mice, was published online May 17 in *Nature*. The senior author is Irving Weissman, MD, professor of pathology and of developmental biology. The lead author is graduate student Sydney Gordon.

PD-1 is a cell receptor that plays an important role in protecting the body from an overactive immune system. T cells, which are immune cells that learn to detect and destroy damaged or diseased cells, can at times mistakenly attack healthy cells, producing autoimmune disorders like lupus or multiple sclerosis. PD-1 is what's called an "immune checkpoint," a protein receptor that tamps down highly active T cells so that they are less likely to attack healthy tissue.

How cancer hijacks PD-1

About 10 years ago, researchers discovered that cancer cells learn to use this immune safeguard for their own purposes. Tumor cells crank up the production of PD-L1 proteins, which are detected by the PD-1 receptor, inhibiting T cells from at- See PD-1, page 7

Scientists crowdsource data to pinpoint autism resource gaps in U.S.

By Erin Digitale

A new crowdsourcing tool aims to map all the locations in the world, beginning with the United States, where individuals with autism live to determine which communities need more resources for diagnosis and treatment of the condition.

Dennis Wall

The tool, called GapMap, was developed at the School of Medicine and is described in a study published online May 4 in *JMIR Public Health and Surveillance*.

Data from an early version of GapMap show that people living near autism diagnostic centers are more likely than those who live far away to have been diagnosed with autism, indicating likely inequities in who gets diagnosed.

The data also show that there are far fewer U.S. autism treatment centers than See GAPMAP, page 7

Counting down days to opening of expanded children's hospital

By Samantha Dorman

Lucile Packard Children's Hospital Stanford is counting down to the debut of its new pediatric and obstetric hospital campus, slated to open in December.

With a mission to lead the way in family-centered care, the Packard Children's expansion will more than double the size of the existing campus by linking the original hospital with a new main building, bringing the total hospital space to 844,000 square feet.

"This will be the nation's most technologically advanced, environmentally sustainable and family-friendly hospital for children and expectant mothers," said Christopher Dawes, chief executive officer. The top-ranked children's hospital in Northern California is at the center of the Stanford Children's Health enterprise, which is the largest health care system in the Bay Area exclusively dedicated to pediatric and obstetric care.

The 521,000-square-foot addition to the hospital and surrounding 3.5 acres of green space and gardens were designed in partnership with patients, families and every level of hospital staff and faculty to ensure all areas of need were accounted for.

"When my mother founded this hospital, she envisioned a place where children and families could receive truly healing care," said Susan Packard Orr. "She saw the power that nature had to heal and uplift. I'm proud that we have carried her vision forward, with world-class sustainability and holistic elements throughout the new hospital. Everything we do at this hospital will have an eye to ensuring that generations to come will be healthier."

Fundraising campaign

Community support played a key role in making this growth possible. The "Breaking New Ground" campaign, which ran from 2007 to 2012 under the volunteer leadership of Anne Bass, Elizabeth Dunlevie and Orr, raised $262 million for the new building and grounds. Further funding will come from hospital income and operating services, public bond money and ongoing community support.

The new facility in Palo Alto will add 149 patient beds and six state-of-the-art operating suites, with a design that allows room to grow as demand increases.

"In our 25 years, we've become leaders in providing the best care for children and expectant mothers. Keeping pace with the growing needs of our patients was the catalyst for this transformation," said Dawes. "We'll continue to build world-renowned programs as part of Stanford Medicine and advance research in every pediatric and obstetric specialty."

Advanced technology

With 13 surgical suites, the new Packard Children's will have more operating rooms than any children's hospital in Northern California, reducing scheduling delays and long waits when surgeries take longer than planned.

A neuro-hybrid surgery suite — the only one of its kind in a California children's hospital — will feature a state-of-the-art diagnostic MRI, direct access to angiography imaging equipment and a full operating room. The suite will enable surgeons to view updated images during surgery and reimage patients before closure of the surgical incision. For a patient having a tumor removed, their surgical team will be better assured of the procedure's success. Ultimately, this will reduce the number of procedures, which in turn will impact overall cost and the amount of time a young patient will spend under anesthesia.

A holistic approach

Planning for emerging technology was integral to the design for the new hospital.

"When planning and design began many years ago, we knew we had to leave room for ever-evolving technology," said Dennis Lund, MD, chief medical officer. "So, we'll have the most advanced capabilities available when we open later this year, with the ability to implement emerging technologies in the future."

The new facility will also have a dedicated isotope radiation therapy room for cancer patients, as well as one of the nation's only stand-alone combined PET/MRI scanners dedicated to pediatric patients. The hybrid scanner combines the two modalities, positron emission tomography imaging and magnetic resonance imaging, into a single scan, allowing physicians to see how diseases are behaving in the body, monitor the effects of treatment and craft informed treatment plans to cater to the patient's case.

Planning for the new Lucile Packard Children's Hospital was done by HGA Architects and Engineers, and the building's design by Perkins+Will, with a central theme of enabling a holistic approach to healing.

"From the beginning, the vision for expansion was founded not only in a mission to lead the way in children's health, but also to nurture the whole family," said Kelly Johnson, PhD, RN, vice president of patient care services and chief nursing officer. "Many of our patients require acute and chronic care, and the hospital becomes a second home for the entire family."

Private patient rooms will be more spacious, with sleeping accommodations for two family members and amenities like laundry facilities and family kitchens on every floor. Special features that help make the space unique and kid-friendly include a large digital, interactive wall as well as a dedicated broadcast studio where children can create, record and edit video content that can be shared in patient rooms throughout the hospital.

Because Packard Children's believes that a holistic approach to health leads to better health outcomes, nature is a vital thread throughout the hospital's campus. Surrounding the new building, 3.5 acres of gardens and green spaces will reflect the flora and topography of Northern California. The hospital's Dunlevie Garden will feature educational and engaging sculptures for children to physically explore.

"We want to give families moments of relaxation, play and discovery, which are so important in the midst of illness and hospitalization," explained Elizabeth Dunlevie, a longtime hospital supporter, board member and chair of the expansion's design task force. "Through walking paths, whimsical sculptures and interactive artwork, children and parents can share time together in an outdoor play environment while still being within the hospital site."

Sustainable design

Inside the hospital, the signage and interior design will reflect California's ecosystems. Each floor will feature overlook areas with views of the landscape, and there will be a planter box in the window of every patient's room to provide a connection to nature for everyone.

Packard Children's will set the standard for sustainability in hospital design. Water conservation, renewable energy use, recycling programs, green housekeeping and local food offerings are all integral to the new Packard Children's.

Water-efficient landscapes and collection systems are expected to save 800,000 gallons of water each year. By using equipment specifically designed to conserve, Packard Children's expects to use 38 percent less water than comparable hospitals. By implementing energy innovations such as an external-shading system, the new building's thermal energy consumption is expected to be 60 percent less than that of similarly sized hospitals in the region.

Transforming original building

The new building will allow for a transformative renovation of much of the existing hospital's space, including the Johnson Center for Pregnancy and Newborn Services into mostly private obstetrics rooms. Some major programs will grow and transition into the new, main building, including the Bass Center for Childhood Cancer and Blood Diseases, the Pediatric Transplant Center and the Betty Irene Moore Children's Heart Center. Additionally, services previously shared with Stanford Hospital will now have a dedicated presence inside the children's hospital, including nuclear medicine, catheterization labs, interventional radiology and patient food services.

Packard Children's growth is connected with the advancement of adult care through the new Stanford Hospital, which is expected to open in 2018.

"An integral part of Stanford Medicine, the expanded Lucile Packard Children's Hospital will help us continue to provide the best possible care for children and pregnant women," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "The new hospital's innovative technology, family-centered design and advanced sustainability features will further advance our academic mission and vision for precision health — enabling us to offer the highest levels of predictive, preventive and personalized care to all of our patients."

"We are all working with focused dedication and excited anticipation as we move toward the opening of our new campus," said Dawes. "Together, we are advancing a vision to heal humanity through science and compassion, one child and family at a time." **ISM**

PERKINS+WILL

The expansion of Packard Children's Hospital will include 3.5 acres of gardens and green spaces, providing relaxing areas for young patients and their families.

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STANFORD MEDICINE

Study discovers first possible drug treatment for lymphedema

By Tracie White

Tracey Campbell has lived for seven years with lymphedema, a chronic condition that causes unsightly swelling in her left leg.

The disease, which stems from a damaged lymphatic system, can lead to infections, disfigurement, debilitating pain and disability. There is no cure. The only available treatment is to wear compression garments or use massage to suppress the swelling, which can occur throughout the body in some cases. Campbell — who had two quarts of excess water in her left leg by the time she was diagnosed — has for years worn restrictive garments 24 hours a day and has spent an hour each night massaging the lymph fluid out of her leg.

Lymphedema is uncomfortable, exhausting and dangerous if left uncontrolled. As many as 10 million Americans and hundreds of millions of people worldwide suffer from the condition, many from the after-effects of cancer therapy treatments.

"There's this extra layer of emotional burden," said Campbell, who added that she has to be constantly vigilant to protect against infection. "All you want to be is normal."

Now there's new hope for a possible pharmaceutical treatment for patients like Campbell. A study led by scientists at the Stanford University School of Medicine has uncovered for the first time the molecular mechanism responsible for triggering lymphedema, as well as a drug with the potential for inhibiting that process.

The study was published May 10 in *Science Translational Medicine*.

"We figured out that the biology behind what has been historically deemed the irreversible process of lymphedema is, in fact, reversible if you can turn the molecular machinery around," said Stanley Rockson, MD, professor of cardiovascular medicine and the Allan and Tina Neill Professor of Lymphatic Research and Medicine at Stanford. Rockson shares senior authorship of the study with Mark Nicolls, MD, professor of pulmonary and critical care medicine. Stanford research scientists Wen "Amy" Tian, PhD, and Xinguo Jiang, MD, PhD, share lead authorship of the study and are also affiliated with the Veterans Affairs Palo Alto Health Care System.

'Fundamental new discovery'

"This is a fundamental new discovery," said Nicolls, who is also a researcher at the VA Palo Alto.

The researchers found that the buildup of lymph fluid is actually an inflammatory response within the tissue of the skin, not merely a "plumbing" problem within the lymphatic system, as previously thought.

Working in the lab, scientists discovered that a naturally occurring inflammatory substance known as leukotriene B4, or LTB4, is elevated in both animal models of lymphedema and in humans with the disease, and that at elevated levels it causes tissue inflammation and impaired lymphatic function.

MARK WILLIAMS

Tracey Campbell suffers from lymphedema and is participating in a clinical trial of a drug to determine whether it can treat the painful condition.

Further research in mice showed that by using pharmacological agents to target LTB4, scientists were able to induce lymphatic repair and reversal of the disease processes.

"There is currently no drug treatment for lymphedema," Tian said. Based on results of the study, the drug bestatin, which is not approved for use in the United States but which has been used for decades in Japan to treat cancer, was found to work well as an LTB4 inhibitor, with no side effects, she said.

Based on the research, bestatin (also known as ubenimex), is being tested in a clinical trial that started in May 2016 — known as ULTRA — as a treatment for secondary lymphedema, which occurs because of damage to the lymphatic system from surgery, radiation therapy, trauma or infection. Primary lymphedema, on the other hand, is hereditary. The results of the research pertain to both types.

Rockson is principal investigator for this multisite phase-2 clinical trial.

"The cool thing about this story — which you almost never see — is that a clinical trial testing the therapy has already started before the basic research was even published," Nicolls said. "This is the first pharmaceutical company-sponsored trial for a medical treatment of lymphedema, a condition that affects millions."

Nicolls and Tian are co-founders of Eiccose LLC. Eiccose is now part of Eiger BioPharmaceuticals, which gets the drug from Nippon Kayaku in Japan. Eiger is sponsoring the clinical trial. Nicolls and Rockson are both scientific advisers to the company.

Two labs, two diseases

The study, which got underway about four years ago, began somewhat uniquely as a collaboration between two labs that were studying two completely different diseases. At the time, the Nicolls lab, where Tian works, was studying pulmonary hypertension. The Rockson lab was conducting lymphedema research.

The two teams met through SPARK, a Stanford program designed to help scientists translate biomedical research into treatments for patients.

"I was in a privileged position of seeing two faculty conducting important research and recognizing the possible link in causality," said Kevin Grimes, MD, associate professor of chemical and systems biology and co-founder of SPARK. "It occurred to me that both diseases affected vascular tissues and had strong inflammatory components."

"He blind-dated us," Nicolls said. "When Amy Tian and I looked at the data from Stan's research, Amy said, 'It looks like it could be the same molecular process.'"

"It was an arranged marriage between us and Stan which worked out great," Tian said.

At the time, Rockson had begun to suspect that lymphedema was an inflammatory disease. This led to his team's discovery that the anti-inflammatory drug ketoprofen successfully helped to relieve lymphedema symptoms, although it wasn't a perfect drug; side effects were a concern, and it remained unclear how the drug worked at the molecular level.

"There's an extra layer of emotional burden."

Meanwhile, the Nicolls lab had discovered that LTB4 was part of the cycle of inflammation and injury that keeps pulmonary hypertension progressing. When researchers blocked LTB4 in rats with the disease, their symptoms lessened and blood vessels became less clogged, lowering blood pressure in the lungs.

"When we became aware of Mark's work, we began to realize that we were both possibly dealing with the activation of steps downstream of the 5-LO [5-lipoxygenase] pathway," Rockson said. "This became intriguing and formed the basis of our relationship."

Joining forces

The two teams joined forces to figure out the mechanism that triggered lymphedema, hopefully revealing a target for drug treatment in humans. After determining that ketoprofen was primarily working on the 5-LO pathway, the researchers began blocking the various endpoint pathways after 5-LO activation in mouse models of lymphedema, Rockson said.

"It turned out that, in fact, we were both dealing with the same branch, which is LTB4," Rockson said.

"So now it became clear we really were dealing with a very similar biological process in two different diseases," he said. "Because of Mark's work in pulmonary hypertension, we knew that we had an ideal form of therapy that we could try in lymphedema as well."

The Nicolls lab had used the drug bestatin, which blocks the enzyme that generates LTB4, to reverse pulmonary hypertension disease processes. When researchers tested bestatin in the mouse lymphedema model, it worked to reverse symptoms of that disease.

"I'm still in awe," Rockson said. "There are few situations where you take a problem at the bedside, and go into the lab, and then take discoveries back to the bedside. It's amazingly gratifying."

Campbell, who is now participating in the double-blinded, placebo-controlled bestatin trial at Stanford, remains hopeful.

"When all of the sudden one of your limbs begins to swell, you want to understand what the heck is going on," she said. "It's a tough condition that few people seem to care about, even though millions and millions suffer with it. We're hoping for something that gives some relief."

Other Stanford authors are research associate Jeanna Kim; former medical students Adrian Begaye, MD, and Abdullah Feroze, MD; Roham Zamanian, MD, associate professor of medicine and director of the Adult Pulmonary Hypertension Service; Gundeep Dhillon, MD, associate professor of medicine and medical director of the Stanford Lung Transplant Program; and research assistants Eric Shuffle and Allen Tu. Shuffle and Tu are affiliated with both Stanford and the VA Palo Alto.

Researchers at Georgia Insitute of Technology, Virginia Commonwealth University, the University of Michigan Health Systems and the University of Illinois at Chicago are also co-authors.

Eiger BioPharmaceuticals has licensed intellectual property developed by Tian, Rockson, Jiang, Kim and Nicolls involving the targeting of LTB4 for the treatment of lymphedema.

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

Strategic planning efforts are launched at Stanford Medicine and the university

By Becky Bach

Stanford Medicine and Stanford University are undergoing separate, but parallel, strategic planning processes, Lloyd Minor, MD, dean of the medical school, and Persis Drell, PhD, university provost, told faculty and staff members at a town hall meeting on campus May 4.

Both efforts began this spring and will wrap up in early 2018, they said.

"Along the way, there will be many opportunities and town hall meetings to engage directly in this process," Minor said.

The Stanford Medicine project — which includes Stanford Health Care, Lucile Packard Children's Hospital Stanford and the School of Medicine — will cover all elements of the three entities' missions — research, education and patient care — but will also take a "deep dive" into several specific areas, such as the desired size of the clinical enterprise.

The project kicked off with a survey, which was completed by 3,769 community members, including 42 percent faculty of members. Facilitators also interviewed 120 people, primarily faculty members but also some staff and other stakeholders, Minor said.

In addition, Stanford Medicine leaders received feedback on the current status of the organization, Minor said.

"When it comes to purpose, we rank significantly above average," Minor said. "The vast majority of people in Stanford Medicine understand and buy into our purpose."

Areas that ranked lower include processes and systems, and the complexity of decision-making — "the general thesis being decision-making is quite complex and often times nebulous," Minor said.

The university's planning process is organized around four general theme areas: education, research, community and beyond the university, Drell said.

The "beyond the university" focus is relatively new, and aims to prompt thought about how Stanford can contribute to the local community, state, nation and world, Drell said. Joseph Woo, MD, professor and chair of cardiothoracic surgery, is the co-chair of that steering group.

The university is welcoming proposals and suggestions from everyone — from faculty to students, Drell said. Suggestions can be submitted by individuals or teams on the project's website. Currently, cost is not being considered, she said. Also, submitting an idea does not make it less likely that another idea is pursued, she said. In other words, the more, the merrier.

"We want the process to be collaborative and inclusive," Drell said. "We have phenomenal individuals in our community."

The task is large, but exciting, she said. "What is the university we want to be in 20 years and how do we get there?" **ISM**

The continuing pursuit of gender parity in academic medicine

By Kathy Zonana

Odette Harris was the only black woman in Stanford School of Medicine's class of 1996. Upon graduation, she became Stanford's sole first-year neurosurgery resident.

"I don't think I've ever been in a professional situation where I wasn't the first or the only," said Harris, MD, now an associate professor of neurosurgery at Stanford, the associate chief of staff for rehabilitation at the Veterans Affairs Palo Alto Health Care System and the director of brain injury programs at both institutions.

As a medical student, Harris had done research with Stanford neurosurgeon John Adler, MD, who likes to warn incoming residents about the grueling program they're embarking on. "He was incredibly candid with me about what people thought about me joining the residency, and he did that in a way not to freak me out or depress me, but he wanted me to have a very real perspective about what I was getting into and not be Pollyanna about it," Harris said. "He was like, 'Listen, I want you to have your guard up.' It was good baggage to carry through residency, to know that I had to be better and to do more."

She knew she was joining a department that had recently been roiled by controversy. In 1991, Frances Conley, MD, the only woman on the neurosurgery faculty — and, in fact, the first female full professor of neurosurgery in the United States — had submitted a letter of resignation after a colleague whose behavior she found demeaning was promoted to acting department chair. After a year of turmoil, the colleague's appointment was reversed and Conley rescinded her resignation, but her revelations of the treatment she and others experienced at the hands of their male colleagues — from exclusion and stereotyping to lewd remarks and unwanted touching — opened up a national conversation about women and sexism in academic medicine.

L.A. CICERO

Sabine Girod helped conduct a study, published in 2016 in *Academic Medicine*, showing that a 20-minute educational intervention could change faculty members' awareness of unconscious bias and their perceptions of female leaders.

Five years later, Harris didn't have much bandwidth to worry about whether she was entering an inhospitable environment. "I was very much aware of what had happened, but I think these are luxury concerns when your biggest concern is, am I going to survive this residency? Are people going to think I'm capable? Are people going to think I'm smart enough?" she said. Even in retrospect, she sees Conley primarily as the inspirational pioneer whose legacy she inherited when she joined the Stanford faculty.

"Fran went through more bullshit than Odette," said Adler, a professor emeritus of neurosurgery who considers Conley a mentor and has himself been a lifelong mentor to Harris. "There was more hostility toward Fran. I know that Odette encountered individual animosity, but it wasn't broad across-the-department hostility.

Today, Stanford's neurosurgery faculty includes 13 women and 43 men in a variety of research and clinical specialties, not all of whom perform surgery. "Nowadays we just expect women to be in the operating room," Adler said. "But even right now, we only have a few women and we should have more. And eventually we're going to."

"'Eventually' is too long to wait," said Hannah Valantine, MD, a cardiologist who served as the School of Medicine's senior associate dean for diversity for many years and is now the chief officer for scientific workforce diversity at the National Institutes of Health. At the current rate of change, without targeted intervention, Valantine has calculated it's going to take more than 50 years before women in the United States achieve parity in academic medicine.

The argument for equal opportunity in academic medicine has moved from "because it's the right thing to do" to "because it's the smart thing to do." Valantine and others who are working to bolster gender equality are increasingly marshaling data in support of their cause: on the benefits of a diverse workforce; on how underrepresented women are in the professoriate and in academic leadership; on the effects of unconscious biases and how to mitigate them; on how best to compensate for differences in how male and female faculty tend to spend their time. After all, they said, they're scientists.

Beyond the pipeline

The gender disparity in academic medicine can no longer be attributed to the so-called pipeline problem: Women make up roughly half of U.S. medical students, and more than half of those receiving PhDs in the biomedical sciences. But they make up 22 percent of the tenured faculty at U.S. medical schools, according to 2013 data from the Association of American Medical Colleges. Their proportion declines as they rise in academic rank: Women are 44 percent of assistant professors — the junior faculty position that represents the first step toward tenure — but only 34 percent of associate professors and 21 percent of full professors. The only rank at which women outnumber men is that of instructor, a separate, non-tenure-track faculty line. And while women are increasingly likely to serve in medical schools' leadership, their numbers in key positions are still small. Nationwide, they make up just 15 percent of department chairs and 16 percent of medical school deans.

"What I hear a lot is, well, we just haven't had women in the pipeline long enough to essentially trickle up," said Diana Lautenberger, the director of women in science at the AAMC. "But if you look at it, women were 40 percent of medical students in 1993. Those women would be in their 50s now, and we don't see anything even close to that percentage in the faculty ranks. So instead of looking at how to get women in the pipeline, because they're already there, we're trying to look at the climate and culture factors that push them out."

Stanford's School of Medicine has made a concerted effort in recent years to increase the diversity of its faculty, including its gender diversity. In 2013, the school exceeded the AAMC's benchmarking data for female faculty: Women were 52 percent of assistant professors, 41 percent of associate professors and 22 percent of full professors. The school had been below the national benchmarks a decade prior. (These numbers have continued to increase; in 2016, they were 56, 44 and 26 percent, respectively.) Women are also rising in the leadership ranks: Today, 27 percent of the departments in the School of Medicine are chaired by women.

> **"If a woman walks into the room, you automatically have a certain set of expectations."**

"We need to build a diverse scientific workforce so that we can serve the needs of our diverse society," said Lloyd Minor, MD, dean of the School of Medicine. "At Stanford, we have the opportunity to be a beacon of excellence in diversity and inclusivity, just as we are a beacon of excellence in science and clinical care."

Having a diverse faculty benefits the research, education and clinical missions of an academic medical center, said professor of pediatrics Yvonne (Bonnie) Maldonado, MD, Valantine's successor as the senior associate dean for faculty development and diversity. "From an academic standpoint, we want to attract the best people. We know that if there are obstacles to women, you can lose up to half of your talented workforce," she said. With respect to clinical care, patient surveys support the value of having a physician workforce that reflects the population it serves, Maldonado said. "People feel comfortable around others with whom they share common experiences or backgrounds," she said. "Gender is a very simple one. Not to say that every woman should have a female physician and likewise for men, but giving patients opportunities to pick from a number of diverse providers is great."

Plugging the leaks

When Mary Hawn, MD, applied for her first faculty job at the University of Alabama-Birmingham, in 2001, a senior faculty member asked, somewhat rhetorically, "Well, should we hire this woman or some guy who's going to come in and do the work?"

"Ultimately, he was my biggest advocate and promoter," said Hawn, now the chair of Stanford's Department of Surgery. His remark has become a longstanding joke between the two of them. "He just laughs, 'Oh, no, did I say that?' And he knows he did," she said.

Hawn has heard it all: "Mostly we're told we don't work as hard, we don't see as many patients, and we're going to need to double the workforce if we keep letting all these women in." In a field where physicians frequently perform procedures, like surgery (as opposed to a less "procedural" field like family practice), those assumptions can be even stronger. "I think to this day, women are discouraged from pursuing highly procedural fields, because of the feeling that the time commitment is more significant and the flexibility is less," Hawn said. "Whenever a woman declares she's interested in being a surgeon or some other intensive specialty, it gets a lot of pushback, and I think it's not intentional. Some of it is just the biases we all have."

Exactly, say researchers. Everyone agrees that women should be in the operating room, but sometimes biases — unconscious ones — get in the way of hiring and promoting qualified women.

"If a woman walks into the room, you automatically have a certain set of expectations — which, by the way, both women and men have," said associate professor of surgery Sabine Girod, MD, PhD, DDS. "For men, there is a positive expectation: He's young but he's a great guy and he will get it done. And for a woman, it's, well, she's young and doesn't have enough experience. This is very soft unconscious bias — I don't think anybody is doing anything on purpose."

Valantine, Girod and colleagues conducted a study, published in January 2016 in *Academic Medicine*, showing that a 20-minute educational intervention could change faculty members' awareness of unconscious bias and their perceptions of female leaders. While she was still at Stanford, Valantine encouraged department chairs to provide this type of information at faculty meetings. "During that period of time, the hiring of

LENNY GONZALEZ

Bonnie Maldonado says that having a diverse faculty benefits the research, education and clinical missions of an academic medical center.

women increased," she said.

Now, every faculty search committee at the School of Medicine receives unconscious bias training at the outset of the search. "People have preconceived notions of who fits a particular job description," said Maldonado, "and when you are able to free yourself to think a little more broadly about whether somebody who would not be a traditional choice for you can fill that position, frequently you can hit pay dirt."

Educating search committees, Valantine said, is only half the battle. The other is to ensure women are applying for tenure-track positions in the first place. "Where in the career path do we lose people?" she asked. "It's that transition into independent careers in academia." Valantine notes that in the biomedical sciences, women make up almost half of postdoctoral scholars but only 25 percent of applicants for assistant professor positions, instead taking jobs in other fields, such as industry or policy. "This is a very scary phenomenon for academic medicine," she said.

The leadership gap

Seven years ago, when Laura Roberts, MD, was offered the position of chair of the Department of Psychiatry and Behavioral Sciences at Stanford, some counseled her not to take it. "People thought that Stanford would not be a supportive environment for a woman leader," she said. "And that's not been the case at all. I've felt incredibly well-supported at Stanford."

Case in point: Shortly after her arrival, Roberts asked for, and received, the approval of university leadership to review the compensation and faculty-line classifications in her department and make adjustments for equity. Then, she expanded its leadership team. "The people who had been leaders in the department were outstanding in every way — they were collaborative and they were lovely to me. They also happened to be from, let's say, a narrow demographic," she said. "They were extraordinary colleagues, and I did not want to signal disrespect or disregard for their great work over many years. Instead, I just elevated other people around them so that our leadership team would reflect the broader perspectives, backgrounds and strengths of our department."

The effect of her larger-than-ordinary leadership team has been salutary. "Our people can see that there are many ways to advance professionally and to become a recognized leader in the department," she said. "We identify positions so that people can apply for them. My sense is that these efforts have lifted morale because the opportunities for promotion and leadership are merit-driven, fair and logical."

That's exactly the kind of transparency that's necessary to get more women into leadership positions in academic medicine, said Girod, who, along with Roberts, represented the School of Medicine on Stanford's Task Force on Women in Leadership. "A lot of women want to do it, but they don't get picked," she said. "When you hire someone for a leadership position, you tend to, because of unconscious bias, pick somebody who is like you. And there are not many women who are picking for these positions, right?"

Roberts is particularly concerned with boosting the number of female department chairs in academic medicine. Although assistant and associate deans are higher on the org chart, the financial power in medical schools is concentrated in departments. "I am happy to see women in visible leadership roles, but I admit that what I really look for is women in leadership roles with actual budgets — women who are enabled to direct resources, to set a vision and allow strategic steps to be taken," Roberts said. "Because that's rare."

Moreover, chairs set the tone for their departments, "from pay equity to culture and climate," said the AAMC's Lautenberger. "We work a lot with the deans and the deans are very much on board, but departments are really like their own independent organizations. They have their own budgets and their own culture and their own structure. Sometimes these departments are largely untouched. It's interesting when you get in there to find climates that are not supportive of gender equity or considering women for leadership positions."

Ensuring a healthy climate was one reason women in Stanford's Department of Surgery banded together and asked to participate in their department's recent search for a new chair. "We said we are 16 female faculty; in the past 10 years, we hired 12 women and 11 women left. It's like a revolving door at the associate and assistant professor levels," said Girod, who, with several colleagues, is completing a study on the reasons why faculty leave the School of Medicine. "The dean and the chair of the search committee were open to that argument, and we actually interviewed every single candidate as a group of women. Then we wrote our recommendations to the dean."

LENNY GONZALEZ

Outside of her work as a neurosurgeon, Odette Harris has made it her mission to improve access to careers like hers, primarily through science outreach to children.

The result of the search: Hawn, whom Girod calls "fantastically qualified — she was really the best of everybody."

Being selected as chair of surgery "validated my contributions were important and impactful, that a traditionally male field would aspire to have a female leader," said Hawn. "I think for the women it's great that they see a woman in charge. I'm curious what it means for the guys. I suspect the relationships are probably a little more formal than they would be with a male chair. But gender isn't the only thing that aligns you with somebody or makes them feel accessible or inspirational."

> **"At Stanford, we have the opportunity to be a beacon of excellence in diversity and inclusivity."**

Hawn looks forward to the day when no one remarks on her gender. "To me, the goal is that there isn't a qualifier," she said. "That you're not a 'woman chair.' That you're not a 'woman surgeon.' That we say, 'Remember the day when we were worried about women being promoted to leadership positions?' Nobody questions a woman's equal right to vote, or admission to college."

Carrying an extra load

Bonnie Maldonado has three children, two of whom were born after she became a faculty member. "How do you deal with going home at night?" she remembered wondering. "How do you balance that?"

The answer came from a more senior colleague, who said, simply, "I don't go to events on evenings and weekends."

In that moment, "I realized it's OK for me to say, 'I really can't go to that event,'" Maldonado said. "I was afraid people would say, well, she just wants to go home and take care of her kids, not be a physician-scientist. And there's no longer a reason to say you have to be one or the other. You should be able to be both."

"If you look at the generation before me, the majority of women who went into surgery never had children," said Hawn, who has two. "They felt like they did have to make a choice."

That was true for Conley, who decided with her husband early on that they would not have children. "You can only have so many lives," she said. "I was really into my neurosurgery program, and it would have taken away from that. I was just so enthralled, to open up the skull and see the brain, the whole soul of the person opened up in front of you."

Roberts, who has six children, called herself a "poster child for everything you're not supposed to do" to be successful in academia. "The decision to have a large family was contrary to all of the advice I received when I was an assistant professor," she said. "Now, everywhere I go, I am told that I am an 'inspiration' because of my dedication to both my children and my career — but at the time, it was hard not to feel like a negative outlier. I had to quickly learn to reject the idea that your personal life and professional life are a teeter-totter in which one must be sacrificed for the other. Doing both fully, and joyfully, has been my intent."

Today, Hawn, Maldonado and Roberts say, both male and female faculty acknowledge greater interest in pursuing work and family goals simultaneously. "The issues that are traditionally thought to be gender-based are actually issues that affect all of us," said Maldonado. "I'm an epidemiologist, and one of the things we learn in training is that outliers can sometimes tell you the key to the problem you're looking at. Since women tended to be the primary caregivers, it seemed to be amplified for women, but it's a problem for everyone."

Women also do more housework, said Girod, citing a 2010 study by Stanford professor of history Londa Schiebinger, PhD, that found that female scientists performed 54 percent of core household tasks, whereas male scientists performed 28 percent. There are also studies showing that female faculty members shoulder a disproportionate share of "academic housework" — work that benefits the institution but does not necessarily advance individual careers, such as committee service, extra teaching responsibilities or student advising.

To address work-life pressures, in 2013-14 Stanford piloted a time-banking program, which provided faculty with credits for such things as serving on committees or providing mentoring. They could exchange those credits for things that would buy them time back at work or at home: say, grant-writing support, housecleaning or meal delivery. Time banking is a better fit for academic culture, Valantine said, than giving people time off in exchange for extra work, or an extra year on the tenure clock after maternity leave. "These integrative policies have to be framed as career advancing, rather than career pausing," she said. "We were able to demonstrate tremendous return on investment." Although the pilot has ended, the Department of Emergency Medicine has chosen to provide time banking for its faculty, and other departments may follow suit.

The next generation

Odette Harris has a pair of photos of the Stanford neurosurgery faculty and residents on her office wall. One day, her two young daughters came in, saw them, and asked, "Mommy, where are the women?"

"I was like, 'What are you talking about?'" Harris said. "And I came over to look at the pictures and I was like, holy crap, you're absolutely right." In the photo from 2003, when Harris finished her residency, there is one other woman, and she's a neurologist rather than a neurosurgeon. In the 2009 photo, from Harris' first year on the faculty, there are a smattering, but again, most of them are not surgeons. In certain surgical specialties, women remain rare.

"The sense of isolation is pretty overwhelming if you don't have the sounding board and the mentorship," Harris said, emphasizing that she herself has felt strongly supported by the senior members of her department. "Everyone needs a sense of community to be able to thrive in this environment." In collaboration with the school's Office of Faculty Development and Diversity, she is spearheading a new program that will create small, supportive groups of women. The office also offers a monthly networking luncheon for all female faculty.

Outside of her work in neurosurgery, Harris has made it her mission to improve access to careers like hers, primarily through science outreach to children. "There are few jobs where you can take the time outside of work to serve on the board of a Boys' and Girls' Club," she said. "Where you can bring in an entire all-girls school to volunteer for a year at the VA when you're a neurosurgeon and some may think your time is better spent in the operating room. I have amazing bosses who authentically support that kind of vision. And to have opportunities like that and still be a neurosurgeon is a dream."

There's only one workplace Harris could combine these threads, she says: academic medicine. "If I have a legacy in the next 30 years, I hope it's my grass-roots efforts to inspire kids," Harris said. "Someday, my children will not be the first or the onlies." **ISM**

Reprinted and edited from the spring 2017 issue of Stanford Medicine *magazine.*

Ketamine

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mission as a physician and researcher."

'Right out of a movie'

Rodriguez's interest in ketamine as a treatment for OCD was sparked about a decade ago when she was first starting out as a research scientist at Columbia University. A small, placebo-controlled study published in 2006 by a mentor of hers, Carlos Zarate, MD, now chief of the section on neurobiology and treatment of mood disorders at the National Institute of Mental Health, had shown that ketamine induced dramatic improvement in treatment-resistant depression within two hours of infusion. It was a landmark study, drawing attention among the psychiatric community and launching a new field of research into the use of ketamine to treat various mood and anxiety disorders.

Rodriguez, intent on searching for better, faster treatment for her patients with OCD, took note. There was an emerging scientific theory that ketamine affects the levels of the neurotransmitter glutamate in the brain and increasing evidence that glutamate plays a role in OCD symptoms, she said. Perhaps ketamine could help regulate OCD symptoms as well as depression.

About three years after Rodriguez's pilot study on the 24-year-old student with OCD, she and colleagues at Columbia published their results from the first clinical trial of ketamine in OCD patients. This trial randomized 15 patients with OCD to ketamine or placebo.

Once again, the effect of ketamine was immediate. Patients reported dramatic decreases in their obsessive-compulsive symptoms midway through the 40-minute infusion, according to the study. The diminished symptoms lasted throughout the following week in half of the patients. Most striking were comments by the patients quoted in the study: "I tried to have OCD thoughts, but I couldn't," said one. Another said, "I feel as if the weight of OCD has been lifted." A third said, "I don't have any intrusive thoughts. ... This is amazing, unbelievable. This is right out of a movie."

"Carolyn's study was quite exciting," Zarate said, adding that there were a number of similar, small but rigorous studies following his 2006 study that found fast-acting results using ketamine to treat bipolar disorder and PTSD.

"We had no reason to believe that ketamine could wipe out any symptoms of these disorders within hours or days," he said.

Search for a safer drug

Virtually all of the antidepressants used in the past 60 years work the same way: by raising levels of serotonin or one or two other neurotransmitters. Ketamine, however, doesn't affect serotonin levels. But exactly what it does remains unclear.

Since coming to Stanford in 2015, Rodriguez has been funded by the National Institute of Mental Health for a large clinical trial of ketamine's effects on OCD. This five-year trial aims to follow 90 OCD patients for as long as six months after they've been given a dose of ketamine or an alternative drug. Rodriguez and her research team want to observe how ketamine changes participants' brains, as well as test for side effects from use of the drug.

Ultimately, Rodriguez said, she hopes the study will lead to the discovery of other fast-acting drugs that work in the brain like ketamine but without its addictive potential.

Recent research in the field indicates that the glutamate hypothesis that triggered her pilot study might be further refined.

"Ketamine is a complicated drug that works on many different receptor sites," she said. "Researchers have fixated on the NMDA receptor, one of the glutamate-type receptors, but it might not be the only receptor bringing benefit."

In May 2016, researchers from NIMH and the University of Maryland — Zarate among them — published a study conducted in mice showing that a chemical byproduct, or metabolite, created as the body breaks down ketamine might hold the secret to its rapid antidepressant actions. This metabolite, hydroxynorketamine, reversed depression-like symptoms in mice without triggering any of the anesthetic, dissociative or addictive side effects associated with ketamine, Zarate said.

"Ideally, we'd like to test hydroxynorketamine and possibly other drugs that act on glutamate pathways without ketamine-like side effects as possible alternatives to ketamine in OCD," Rodriguez said.

Rodriguez is also interested in using ketamine as a way to kick-start a type of cognitive behavioral therapy called exposure and response prevention, an evidence-based psychological treatment designed to help patients overcome their OCD. The therapy involves teaching patients with OCD to face anxieties by refraining from ritualizing behaviors, then progressing to more challenging anxieties as they experience success.

Relaxation and other techniques also help patients begin to tolerate their anxiety — for example, postponing the compulsion to wash their hands for at least 30 minutes, then extending that time period.

"My goal isn't to have people taking ketamine for long periods of time," Rodriguez said. But perhaps a short-term course of ketamine could provide its own kind of exposure and response prevention by allowing patients to experience that it is possible not to be controlled by their OCD, she said.

Almost a decade after her first ketamine pilot study, Rodriguez remains inspired by the magic of seeing the 24-year-old student's eyes light up as the drug alleviated OCD symptoms that had caused her years of daily suffering.

"After the study, I was walking her to her taxi to go home," Rodriguez said. "The side effects of the drug had worn off; she was back to her baseline. I asked what it was like not to have OCD. She said it was the strangest feeling. She could do normal things but without the OCD symptoms. So just the fact that in a matter of hours you can disconnect from OCD makes me a believer.

"I just don't like the idea of people being in pain," Rodriguez said. "I want to see science translated into treatments now." ISM

Ketamine finds market as an off-label option for mental disorders

By Tracie White

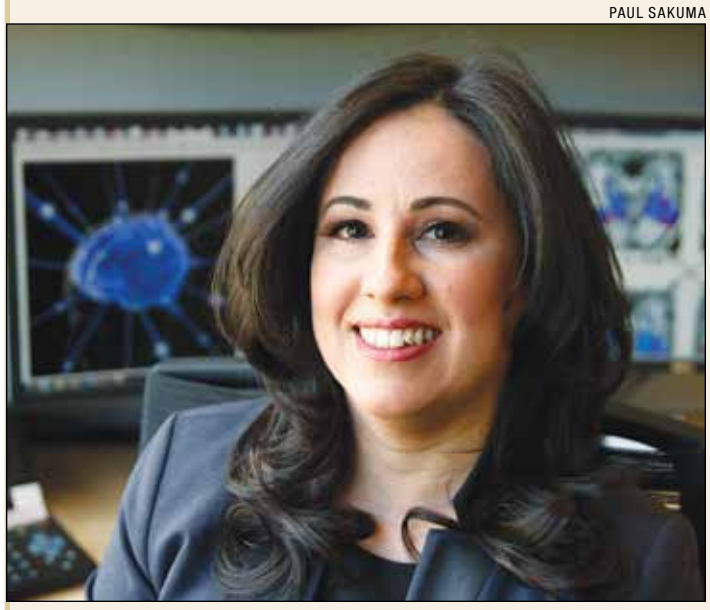
Geuris "Jerry" Rivas, a native of New York, was diagnosed with severe obsessive-compulsive disorder when he was 15. Obsessions with organizing and reorganizing the belongings in his bedroom — posters, comic books, videos — took over most of his day.

Forced by germ obsessions to compulsively wash and rewash his hands, he started wearing gloves all day to both protect him from the germs and stop him from washing his hands raw. Now, at 36, OCD symptoms continue to cost him jobs and relationships. He's managed to turn his organizational skills into a profession — he's a home organizer and house cleaner — but still he struggles daily with his obsessions, missing work, risking relationships.

"It's caused me a great deal of suffering," Rivas said. "I've tried many, many medications. I've wasted so much of my life."

In 2012, running out of answers, Rivas took part in a clinical trial to try ketamine as a treatment for OCD. The trial was run by Carolyn Rodriguez, MD, PhD, then a researcher at Columbia University and now an assistant professor of psychiatry and behavioral sciences at Stanford.

PAUL SAKUMA



Carolyn Rodriguez is researching ketamine's safety as a long-term treatment for OCD.

Life-changing experience

And with a single infusion of the drug, he experienced, for two weeks, what it was like to live without the compulsions and obsessions that had for years controlled his life.

"I felt like, for the first time, I was able to function like a regular person," he said.

Beginning more than a decade ago with a study funded by the National Institutes of Health that showed ketamine infusions inducing dramatic improvements in treatment-resistant depression, ketamine research has burst into the field of psychiatry, spurring studies like Rodriguez's that have shown success in treating OCD, bipolar disorder and post-traumatic stress disorder.

Researchers have a way to go, though, in determining exactly how ketamine works in the brain and whether another drug might be identified or developed that has the same benefit as ketamine without its addictive potential and hallucinogenic effects. Meanwhile, enticed by headlines about the drug's efficacy, private ketamine clinics have begun popping up across the country, making costly new treatments available to patients who are searching for help to stop their suffering now. Ketamine is approved as an anesthetic by the Food and Drug Administration, but insurance companies don't cover its off-label use for mental health disorders. So patients who have run out of treatment options are paying hundreds of dollars a dose for repeated ketamine infusions.

As scientists continue to search for answers about the drug, many patients are already taking the risk of trying it. Advocates say that the dose used for mental health disorders is smaller than that used for anesthesia or by abusers and can be administered safely. But there is evidence from people who abuse the drug routinely — in much higher doses — that chronic, high-frequency ketamine use may be associated with increased risk of cystitis, an inflammation of the bladder, and cognitive impairment, Rodriguez said.

'Desperation of patients'

"The fact that these clinics exist is due to the desperation of patients," said Rodriguez, who is currently researching the drug's safety as a long-term treatment for OCD. Still, she understands what motivates the clinicians to prescribe the drug now to patients in dire straits — those who are suicidal or who have tried every possible medication and therapeutic option and continue to suffer each day.

"I see it as a way to treat people whose OCD is very, very severe," she said. "People who can't come out of the house, who are suicidal, who have no other options."

Janssen Pharmaceuticals is currently conducting a phase-3 clinical trial of ketamine in people with treatment-resistant depression. The company plans to ask the FDA to approve the drug for use in treating this condition.

Alan Schatzberg, MD, a professor of psychiatry and behavioral sciences at Stanford, along with other Stanford faculty including Rodriguez, is investigating the mechanism of action of ketamine in treating depression.

A few academic research institutions have begun offering ketamine treatment to patients, including UC-San Diego and Yale University.

"I think it's a game changer, and it's here to stay," said David Feifel, MD, PhD, professor emeritus of psychiatry at UC-San Diego, who studies the effect of ketamine on clinical depression. Feifel began prescribing the drug for patients with treatment-resistant depression in 2010.

"I've found it to be very safe," Feifel said, adding that the American Psychiatric Association recently issued safety guidelines on how to use ketamine clinically.

"There's a recognition that people like me and others are using the drug to treat patients now," he said. "There's an incredible need for something."

The drug hasn't worked for everyone he's treated, Feifel said, but for many it's been "life-changing."

"I usually tell people to wait and see for 24 hours after treatment," he said. "I had one patient who said she was eating cereal the next day and suddenly it felt like all the lights were popping on in different parts of her brain."

When Rivas, the patient who received a single dose of ketamine during a clinical trial four years ago, heard that certain private ketamine clinics are now offering the drug as treatment for OCD, he said he understands why patients take the risks and pay the high prices. As more research has become available, he's begun considering it himself.

"I've been suffering through my OCD for so long, I've gotten to the point where I'd try anything," he said. ISM

PD-1

continued from page 1

tacking the tumors. In effect, the proteins are a "don't kill me" signal to the immune system, the Stanford researchers said. Cancer patients are now being treated with antibodies that block the PD-1 receptor or latch onto its binding partner, PD-L1, to turn off this "don't kill me" signal and enable the T cells' attack.

"Using antibodies to PD-1 or PD-L1 is one of the major advances in cancer immunotherapy," said Weissman, who is also the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and director of the Ludwig Center for Cancer Stem Cell Research and Medicine at Stanford. "While most investigators accept the idea that anti-PD-1 and PD-L1 antibodies work by taking the brakes off of the T-cell attack on cancer cells, we have shown that there is a second mechanism that is also involved."

What Weissman and his colleagues discovered is that PD-1 activation also inhibits the anti-cancer activity of other immune cells called macrophages. "Macrophages that infiltrate tumors are induced to create the PD-1 receptor on their surface, and when PD-1 or PD-L1 is blocked with antibodies, it prompts those macrophage cells to attack the cancer," Gordon said.

Similar to anti-CD47 antibody

This mechanism is similar to that of another antibody studied in the Weissman lab: the antibody that blocks the protein CD47. Weissman and his colleagues showed that using anti-CD47 antibodies prompted macrophages to destroy cancer cells. The approach is now the subject of clinical trials in human patients.

NORBERT VON DER GROEBEN

"While most investigators accept the idea that anti-PD-1 and PD-L1 antibodies work by taking the brakes off of the T-cell attack on cancer cells, we have shown that there is a second mechanism that is also involved," Irving Weissman, senior author of the new study, says.

As it stands, it's unclear to what degree macrophages are responsible for the therapeutic success of the anti-PD-1 and anti-PD-L1 antibodies.

The practical implications of the discovery could be important, the researchers said. "This could lead to novel therapies that are aimed at promoting either the T-cell component of the attack on cancer or promoting the macrophage component," Gordon said.

Another implication is that antibodies to PD-1 or PD-L1 may be more potent and broadly effective than previously thought. "In order for T cells to attack cancer when you take the brakes off with antibodies, you need to start with a population of T cells that have learned to recognize specific cancer cells in the first place," Weissman said. "Macrophage cells are part of the innate immune system, which means they should be able to recognize every kind of cancer in every patient."

Other Stanford co-authors of the study are associate professor of pathology Andrew Connolly, MD, PhD; visiting scholar Gregor Hutter, MD, PhD; instructor Rahul Sinha, PhD; postdoctoral scholars Roy Maute, PhD, Daniel Corey, MD, and Melissa McCracken, PhD; graduate students Benjamin Dulken, Benson George and Jonathan Tsai; and former graduate student Aaron Ring, MD, PhD.

The research was supported by the D.K. Ludwig Fund for Cancer Research, the A.P. Giannini Foundation, the Stanford Dean's Fellowship, the National Institutes of Health, the Swiss National Science Foundation and the National Center for Research Resources.

Weissman is a founder of the company Forty Seven Inc., which is sponsoring clinical trials of the anti-CD47 antibody.

Stanford's departments of Pathology and of Developmental Biology also supported the work. **ISM**

GapMap

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needed. Across the country, the average demand for treatment is 18 times larger than the available supply of caregivers, the research showed. Prior studies have indicated that the number of children affected by the developmental disorder is still rising.

"There is a growing imbalance between the number of people who need autism care and the number of places that can provide care," said the study's senior author, Dennis Wall, PhD, associate professor of pediatrics and of biomedical data science at Stanford. "It's a geographic distance problem. We need to quantify, in real numbers, the geographic disconnect between people and treatment options so that we can see where the gaps are."

COURTESY OF JMIR PUBLIC HEALTH AND SURVEILLANCE

Stanford researchers want families and caregivers of people with autism to help populate GapMap, which will show the communities where people with autism live and the services available in their areas.

Children who are diagnosed quickly and receive early, intensive autism therapies fare better than those who do not, but parents who suspect that their child has autism often face months-long waits to see caregivers who can make the diagnosis, prior research has found. And current estimates of autism prevalence do not identify geographic gaps in autism resources; the U.S. Centers for Disease Control and Prevention says 1 in 68 children nationwide have autism, but this estimate relies on data from only 11 states. Incidence elsewhere across the globe has not been rigorously established.

Pilot study

The first iteration of GapMap, described in the paper, used data that the researchers collected by programming a web spider to gather information from the websites of 840 autism treatment centers in the United States and 135 centers in the United Kingdom. These were placed onto geographic heat maps of the two countries. Autism prevalence in each part of the United States was estimated by assuming a rate of 1 case of autism per 50 people, and then using U.S. census data to generate a map estimating where people with autism live. Data on people in the United Kingdom with autism was also used to confirm that GapMap works as expected. (Comprehensive data on people in the United Kingdom with autism is already publicly available.)

Across the United States, 70 percent of people live within 30 miles of a diagnostic center, the study found. The average distance from an individual in the United States to the nearest diagnostic center is 50 miles, whereas people who have been diagnosed with autism live on average 20 miles from the nearest diagnostic center. Although the gap may partly reflect that people move closer to diagnostic centers after diagnosis, the researchers also think it reflects lower diagnosis rates among people in rural locations.

"We really need to see where the imbalances are and how big they are."

The latest version of GapMap functions as an interactive site accessible on any internet-connected device. It will help connect families to autism-based resources. In the future, Wall's team will add more functionalities, such as layering the map with environmental factors to understand their impact on autism prevalence. GapMap also aims to create one of the largest databases that will enable families to connect to and participate in current autism research.

'An important unmet need'

"Our findings highlight that there is an important unmet need with respect to individuals in resource-poor areas, where there is a significant lack of autism services," Wall said. "As a consequence, we think they are getting diagnosed later and not reaching the care they need during the time when it matters most."

Now, the researchers are asking families and caregivers to contribute to the database. Individuals with autism and their families can enter basic data about themselves into GapMap, such as their state, ZIP code, gender, birth date and autism diagnosis. They are also asked to answer a short list of questions about the degree to which the person with autism shows traits associated with the disorder. The data are stored in a secure, Health Insurance Portability and Accountability Act-compliant database. Participants have the option to receive notifications inviting them to take part in future research, and can see where other people with autism live. Autism experts can also contribute information about the services they provide.

Wall hopes the database will help build global online communities of families affected by autism, will inform them about resources in their areas and will clarify where more autism treatment centers should be located or where technology-based solutions can be invented to fill the void.

"We really need to see where the imbalances are and how big they are as the first step to creating change in the health care system," he said.

To visit GapMap, go to https://gapmap.stanford.edu.

Wall's Stanford collaborators on the study are former software development intern Nikhila Albert, software developer Michael Du and clinical research coordinators Jena Daniels and Jessey Schwartz.

Wall is a member of Stanford's Child Health Research Institute, which supported the research.

The research was also supported by the Wallace H. Coulter Foundation, Stanford's Beckman Center for Molecular and Genetic Medicine, the Hartwell Foundation and Spectrum, the Stanford Center for Clinical and Translational Research and Education.

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

Stanford Medicine magazine reports on sex, gender and medicine

By Rosanne Spector

The practice of medicine would be so much simpler if humans came in only one sex — and until only recently, most doctors and researchers have behaved as if that were the case. Modern medicine is largely based on what works for men. Doctors are mostly men, new treatments are tested mainly on men, medical school teachers are mainly men. Even lab animals are largely male.

This is starting to change, though gradually. In the new issue of *Stanford Medicine* magazine, you'll find articles about how the medical world has begun to factor not only sex but gender into teaching, research and care — and why it matters.

"Both sex and gender influence human health and disease," said Janine Clayton, MD, the director of the National Institutes of Health's Office of Research on Women's Health, in the article leading off the theme package on sex and gender in medicine.

"It is increasingly clear that it is both an ethical and scientific imperative to conduct research and report on the results for both men and women," she added.

One challenge for researchers is simply measuring gender, said Marcia Stefanick, PhD, director of the Stanford Women and Sex Differences in Medicine Center. It's not as straightforward as most of us think.

"Sex is generally assigned at birth, based on external genitalia, after which a broad range of biological, particularly reproductive, sex differences are assumed. Individuals are then, usually, forced into a binary model of gender — with distinct masculine and feminine categories — when the possibilities are much broader and more expansive," explained Stefanick, in the same article.

She is part of a team developing a way to place an individual's gender on a continuum so it can be accurately correlated to health outcomes.

Also in the issue:

- A Q&A with Barbra Streisand about fighting to end discrimination against women in cardiovascular research and care.
- A story about the state of gender diversity among medical-school faculty and strategies to pick up the pace of change.
- An article describing research into the inherent differences in male and female brains.
- A feature about a transgender teen and the care he received at the new Stanford Children's Health Pediatric and Adolescent Gender Clinic. A video about another transgender teen and his family accompanies the online version of the story.

The issue also includes a story about a researcher who invents "frugal science" tools, like an origami microscope that costs less than $1; and an excerpt from *An American Sickness*, a new book about the ills of U.S. health care, written by Elisabeth Rosenthal, MD, editor-in-chief of *Kaiser Health News*.

The magazine is available online at http://stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at 723-6911 or by sending an email to medmag@stanford.edu. **ISM**

OF NOTE

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

STEVE ASCH, MD, professor of medicine, was appointed as one of three editors-in-chief of the *Journal for General Internal Medicine*, which publishes research on primary care, health services, implementation science, medical education and the humanities. Asch specializes in improving and understanding care quality.

PAUL BOLLYKY, MD, PhD, assistant professor of medicine and of microbiology and immunology, was named a 2017 Scholar-Innovator by the Harrington Discovery Institute. Bollyky receives at least $100,000, as well as assistance with drug development and project management to support breakthrough discoveries characterized by innovation, creativity and potential clinical impact. Bollyky was selected for his work on a new drug for Type 1 diabetes.

KARL DEISSEROTH, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences, has received the Distinguished Redelsheimer Award from the Society of Biological Psychiatry. The $50,000 award recognizes a major breakthrough in the science of biological psychiatry. Deisseroth is being honored for his work in optogenetics, for developing CLARITY and for advancing the understanding of neuroscience. He holds the D.H. Chen Professorship.

ANDREW HUBERMAN, PhD, associate professor of neurobiology and of ophthalmology, has received the Cogan Award from the Association for Research in Vision and Ophthalmology. The award is given to a researcher younger than 45 who has made important contributions to ophthalmology research and who shows substantial promise. Huberman was honored for his work studying the development, function and repair of mammalian visual circuits. He is investigating how to regenerate the diseased and injured visual system.

Steve Asch

JULIA KALTSCHMIDT, PhD, was appointed associate professor of neurosurgery, effective April 1. Her research focuses on the mechanisms driving mammalian neuronal circuit formation.

NIC DURHAM

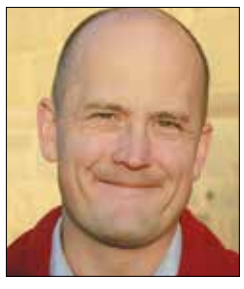
Why did the tree cross the road?

A coast live oak, or *Quercus agrifolia*, estimated to be between 100 and 150 years old has been moved to a plot of land just across Pasteur Drive from where it stood near the Center for Clinical Sciences Research building. Weighing more than 550,000 pounds, the tree was relocated earlier this month to make room for the planned BioMedical Innovations Building, where researchers will work on turning discoveries into treatments and cures.

STEVEN LIN, MD, clinical assistant professor of medicine, has received the President's Award from the Society of Teachers of Family Medicine for his work on its Faculty for Tomorrow Task Force, which focused on strategies to remedy the shortage of faculty members in family medicine. Lin was also appointed to the organization's board of directors. He is the medical director of Stanford Family Medicine.

DAVID A. STEVENSON, MD, was promoted to professor of pediatrics, effective April 1. He is the program director for the medical genetics residency and the combined pediatrics-medical genetics residency program. He also co-directs the genetics testing optimization service. His clinical focus is on RASopathies and vascular disorders. His research focuses on the impact of the Ras/MAPK pathway on musculoskeletal disorders.

CORNELIA WEYAND, MD, professor of medicine, was selected as the 2017 David Trentham Visiting Professor in Rheumatology at Harvard University. As part of her visit in March, she gave a presentation on medium- and large-vessel vasculitis. Weyand is the chief of the division of immunology and rheumatology. Her interests include telomere biology and the role of genomic stress on autoimmunity and inflammation. **ISM**

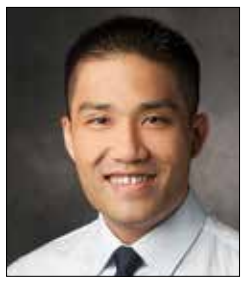


Paul Bollyky

Karl Deisseroth

Andrew Huberman

Julia Kaltschmidt



Steven Lin

David A. Stevenson

Cornelia Weyand