INSIDE STANFORD MEDICINE

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Stanford has opened a lab that makes cell- and virus-based therapies for use in humans.

Page 4

In rite of passage, students meet cadavers

By Tracie White

The first day in the anatomy lab begins with a moment of silence in honor of the donated bodies lying hidden inside plastic blue bags on shiny, clean metal tables.

Then the bags are unzipped.

It's one of the essential firsts of becoming a doctor at the School of Medicine: Cutting into your cadaver in Surgery 203, Clinical Anatomy, surrounded by a team of fellow first-year medical students, sharing both excitement and trepidation as the journey to becoming a physician begins.

"Why learn anatomy?" said Sakti Srivastava, MD, associate professor of surgery and an instructor of the anatomy course, during the lecture that preceded the visit to the lab. "It's the quintessential medical school course. It's an experience you will probably remember the rest of your life."

On Aug. 30, this year's class of 93 new medical students met the cadavers that they will be dissecting over the course of the next seven months. The experience followed a series of firsts for the students: dressing in clean blue scrubs in preparation for lab; meeting fellow classmates during a camping trip to Stanislaus National Forest the week before; being awarded white coats and stethoscopes during a ceremony the afternoon of Aug. 26 on Alumni Lawn.

"There's no doubt you are brilliant and driven," Lloyd Minor, MD, dean of the School of Medicine, told the class at the ceremony. "You were selected from a pool of 7,500 applicants, making this year's 2.3 percent acceptance rate one of the most competitive we've ever had." The new class is comprised of 47 women and 46 men. Four have doctorates and nine have master's degrees; 25 were born outside of the United States; 44 have studied abroad; 13 played varsity sports in college; and about one-third play a musical instrument.

And most, it seemed, had prepared in some way for the first day of anatomy lab.

ROD SEARCEY

Students attend their first lecture in Clinical Anatomy on Aug. 30 shortly before being introduced to the cadavers they will be dissecting.

Nerves and anticipation

"I have mixed feelings," said Victor Contreras, a student from San Diego, the morning before the lab. "I'm obviously very excited. At the same time, I'm kind of nervous. This is a human person. This is someone's loved one. I'll basically be cutting them up."

"I'm looking forward to it simulating a relationship with real patients," said medical student Maria Interrante, who attended Stanford as an undergraduate. "We will be introduced to the cadaver as a person. I think it's one of the most important parts of medical school."

During the Aug. 30 anatomy lecture, students were prepped for the dissection of the chest. They learned the number of ribs — 12 — and the different type of ribs: floating, false and true ribs. They learned the names and locations of the bones in the chest, and much more. Then, they walked next door to the anatomy lab, found their lockers, pulled on their purple gloves and prepared themselves to peek inside a human chest.

"We'll be looking inside somebody who gave their life and their body," said Osama El-Gabalawy, anxiously awaiting the unveiling of his cadaver.

Team support

The students crowded around their assigned lab tables, rolled back the blue body bags and got to work. First they assembled their scalpels, then looked nervously at each other. In a corner of the room at table 3, where Contreras was assigned, teammate Ryan Brewster made the first incision into the team's cadaver. With a firm hand, he sliced down from the jugular notch to the xiphoid process, the lowest part of the sternum. And then one by one, the

See ANATOMY, page 6

Retinoic acid found to suppress colorectal cancer development

By Krista Conger

Retinoic acid, a compound derived in the body from vitamin A, plays a critical role in suppressing colorectal cancer in mice and humans, according to researchers at the School of Medicine.

Mice with the cancer have lower-than-normal levels of the metabolite in their gut, the researchers found. Furthermore, colorectal cancer patients whose intestinal tissues express high levels of a protein that degrades retinoic acid tend to fare more poorly than their peers.

The research is the first to unravel a complicated dance between retinoic acid levels, immune-related inflammation and gut microorganisms. It may suggest new ways to prevent or treat colorectal cancer in humans.

"The intestine is constantly bombarded by foreign organisms," said Edgar Engleman, MD, professor of pathology and of medicine. "As a result, its immune system is very complex. There's a clear link in humans between inflammatory bowel disease, including ulcerative colitis, and the eventual development of colorectal cancer. Retinoic acid has been known for

See RETINOIC ACID, page 6

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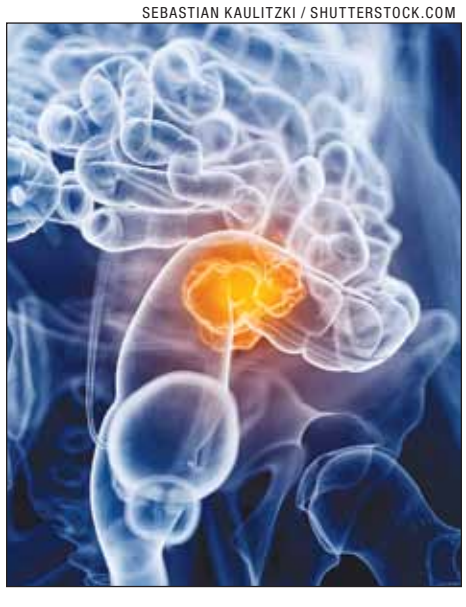

Investigators identify brain circuit that drives sleep-wake cycle

By Bruce Goldman

School of Medicine scientists have identified a brain circuit that's indispensable to the sleep-wake cycle. This same circuit is also a component of the reward system, an archipelago of interconnected brain clusters crucial to promoting behavior necessary for animals, including humans, to survive and reproduce.

It makes intuitive sense that the reward system, which motivates goal-directed behaviors such as fleeing from predators or looking for food, and our sleep-wake cycle would coordinate with one another at some point. You can't seek food in your sleep, unless you're an adept sleepwalker. Conversely, getting out of bed is a lot easier when you're excited about the day ahead of you.

But until this study, no precise anatomical location for this interaction between the brain's reward and arousal systems has been pinpointed, said Luis de Lecea, PhD, professor of psychiatry and behavioral sciences.

ADA EBAN-ROTHSCHILD

Researchers found that when a brain circuit in mice was suppressed, they built nests and went to sleep.

The researchers' findings were published online Sept. 5 in *Nature Neuroscience*. De Lecea

See SLEEP, page 7

More chemo drugs don't improve treatment of rare bone cancer

By Erin Digitale

Adding two chemotherapy drugs to the standard treatment for a rare bone cancer did not improve patients' outcomes and increased toxic side effects, a study of more than 600 patients in 17 countries has found.

The study, which was published Aug. 25 in *The Lancet Oncology*, provides the first head-to-head comparison of two chemotherapy regimens that have been widely used to treat osteosarcoma, a malignant bone tumor. The disease affects about 600 U.S. patients per year, mostly teenagers. Current treatments enable only 65 to 70 percent of patients to live three years past diagnosis without relapse or second cancers, prompting researchers to look for better therapies. Previous small, non-randomized studies suggested that more aggressive chemotherapy with extra drugs might aid some patients, but the new data indicated no benefit from this approach.

"This trial matters because, in the past, we were treating a lot of patients with these drugs without realizing that they weren't helping," said the study's lead author, Neyssa Marina, MD, professor of pediatrics at the School of Medicine.

The rarity of osteosarcoma meant that a large, international collaboration was needed to gather enough patients for a rigorous comparison of the two drug regimens. Doctors at Lucile Packard Children's Hospital Stanford, where Marina is a pediatric oncologist, treat about five to six cases per year, and other large cancer centers have similar numbers of patients.

Most osteosarcomas occur in growing bone, often in the long leg bones near the knee. Treatment consists of chemotherapy to try to kill the tumor, followed by surgery to remove it and then more chemotherapy to get rid of any remaining cancer cells. If the tumor is not at least 90 percent dead when it is surgically removed, the patient has a worse long-term prognosis. Such patients were the focus of the new trial.

Comparing drug combinations

Neyssa Marina

The trial compared two drug combinations. The first, known as MAP, combines methotrexate, doxorubicin and cisplatin. It is the standard osteosarcoma treatment. The second combination, MAPIE, adds the drugs ifosfamide and etoposide. All 618 patients studied had two rounds of MAP chemotherapy followed by surgery, and all were found to have less than 90 percent dead tumor at surgery. After surgery, 310 patients were randomized to receive MAP, while 308 received MAPIE. The trial followed patients for an average of five years and measured "event-free survival," which is the time to a recurrence of the cancer, a second malignancy or death. Treatment side effects were also recorded. MAPIE did not lengthen event-free survival and caused more side effects than MAP.

"The important message from this data is that adding these two drugs does not improve the outcomes of patients who have poor responses to the initial chemotherapy," Marina said. "The drugs shouldn't be added. With them, patients experience more toxicity and more second malignancies." The data is already changing pediatric cancer care, she added.

The research team believes the next advances in osteosarcoma therapy will require a precision-medicine approach that finds and targets specific cancer-causing gene mutations in different patients, Marina said.

The paper's senior authors are Matthew Sydes of University College London and Jeremy Whelan, MD, of University College Hospital, London. Heike Daldrup-Link, MD, associate professor of radiology at Stanford, is a co-author of the study. The paper's 53 authors also include scientists in Austria, Belgium, Canada, the Czech Republic, Denmark, Germany, Hungary, the Netherlands, Norway, Sweden, Switzerland, the United Kingdom and throughout the United States.

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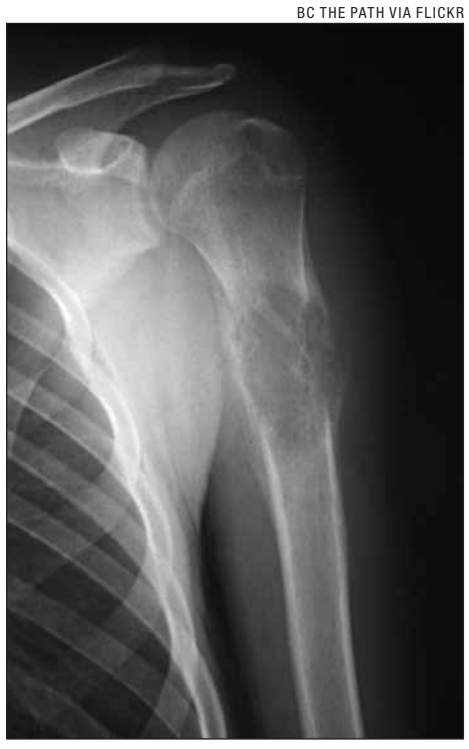

An image of an osteosarcoma on an arm bone.

Funding for the trial was provided by the U.S. National Cancer Institute and the European Science Foundation, with additional international support.

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

Physician advice to patients on e-cigarettes varies, reveals knowledge gaps

By Sarah C.P. Williams

If you ask two different doctors about e-cigarettes, you might get two different answers.

Whether you want to know about the safety of the devices — which create an inhalable aerosol from heated liquid nicotine and flavoring — or how to use them to quit smoking tobacco cigarettes, physicians range greatly in their responses to patients.

That's one finding from a new study by researchers at the School of Medicine who analyzed more than 500 online interactions between patients and doctors discussing e-cigarettes. The study was published online Aug. 26 in the *American Journal of Preventive Medicine*.

"Researchers have previously surveyed doctors about their knowledge and attitudes concerning e-cigarettes. In this study, we were curious about actual provider behavior — the advice doctors gave in real patient interactions," said the study's senior author, Judith Prochaska, PhD, MPH, associate professor of medicine at the Stanford Prevention Research Center. "Within a novel online medical forum, we were able to observe the exact advice doctors were giving patients and see how that advice varied by topic and clinician."

The new observations have already helped inform the development of an educational portal, by Prochaska and colleagues, which aims to teach doctors what's known about the health effects of e-cigarettes and how to communicate the benefits and risks of the devices to patients. Available online through the Stanford Center for Continuing Medical Education, the interactive program provides clinicians with continuing medical education credits.

A growing trend

While traditional cigarettes deliver nicotine to a person's body when they inhale burning tobacco, e-cigarettes work by heating up liquid until it vaporizes. E-cigarette use among both adults and teenagers has risen quickly in the decade since coming on the market. According to the latest estimates from the U.S. Centers for Disease Control and Prevention, 3.7 percent of U.S. adults regularly use e-cigarettes. The devices are often promoted as safer than combustible cigarettes, and are also suggested as a smoking cessation aid, yet there's little long-term evidence to support either assertion.

"There's been rapid growth in the promotion and use of the products without an evidence base in terms of their safety and efficacy for tobacco cessation," Prochaska said.

Judith Prochaska

Because e-cigarettes are so new, and so few studies have been conducted on them, physicians have little to rely upon when patients ask about the devices. For this reason, Prochaska and her colleagues wondered what doctors typically said, and whether they conveyed that uncertainty.

"The big question for me, working in tobacco control, is what's the best way for physicians to counsel their patients about electronic cigarettes," said postdoctoral scholar Cati Brown-Johnson, PhD, a co-lead author of the new paper.

A new source of data

Prochaska and Brown-Johnson teamed up with researchers at HealthTap, an online health company that allows users to submit medical questions which are answered by any of the 72,000 licensed physicians that work with the site.

"Outside of sitting and watching years of live interactions between patients and providers, this was really the best way for us to get data," said Brown-Johnson.

When the scientists searched through all the anonymous questions posted on the site from July 2011 through June 2015, they identified almost 10,000 that related to tobacco or smoking. Of those, about 500 mentioned e-cigarettes — and the rate of e-cigarette-related questions increased over the four-year time period.

The questions ranged from the straightforward, like "Are e-cigs unsafe and can they become addictive?" to more specific concerns, including "Does nicotine/e-cigs cause hair loss?" and "Can vapor cigarettes affect asthma?" Overall, about 34 percent of the questions related to specific side effects and harms of e-cigarettes, 27 percent to general safety and 19 percent to use of e-cigarettes as quitting aids.

For each question and answer, the researchers analyzed what themes were mentioned by patients and physicians, whether the answers were negative or positive about e-cigarettes in tone and message, and whether patients clicked a button to thank the provider for their answer.

Mixed messages

The most frequent themes brought up by physicians matched the most frequent concerns of patients: specific side effects and general safety. But doctors also often brought up topics not mentioned by patients, including the need for more research on e-cigarettes and the relative safety of e-cigarettes compared with combusted tobacco. In addition, clinicians tended to mention nicotine more often than patients, with an expressed concern about addiction.

And when it came to the overall tone of the physicians' answers, there was a range: 47 percent of answers were deemed by the researchers as being negative regarding e-cigarettes — for example, focusing on risks of the devices and discouraging patients from using them. Another 20 percent were positive — for example, encouraging the use of e-cigarettes as smoking cessation aids.

When asked specifically about quitting smoking, 54 percent of doctors mentioned e-cigarettes as a potential tool.

"The existing research, however, does not indicate that e-cigarettes help people quit combustible cigarettes," Prochaska said. "This is an area in need of greater study."

When the researchers looked at how

See E-CIGARETTE, page 3

INSIDE STANFORD MEDICINE

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STANFORD MEDICINE

Egyptian women say doctors don't discourage genital cutting

By Ruthann Richter

Women in Egypt are seeking out doctors' opinions on whether they should circumcise their daughters and, though it is illegal there, physicians are not discouraging the practice, giving legitimacy to a procedure that has serious medical risks, according to a new study led by a former School of Medicine researcher.

Rates of female circumcision, also known as female genital mutilation or female genital cutting, have rapidly declined in Egypt in recent years as a result of women's empowerment and mass media campaigns that highlight the potential health risks of the procedure, which include infection, hemorrhage and death, said the study's lead author, Sepideh Modrek, PhD, who was an instructor in medicine at Stanford when the work was conducted.

Among the 410 women interviewed in the study, about one-third said they were uncertain about the need for the procedure and/or were worried about the risks for their daughters, so they sought out doctors for advice, the study showed. Most women who said that they would follow through with the procedure for their daughters were having it done by physicians, rather than traditional midwives, as a safety precaution, the researchers found.

MAIA SIEVERDING

A 2013 photo of a billboard next to a major highway in Egypt that calls for "the beginning of the end" of female circumcision as part of a national campaign against the practice.

"We found that it's true some women were planning to do it [cut] anyway and are just going to the doctor for harm reduction," said Modrek, who is now an assistant professor of economics at San Francisco State University and a visiting scholar at Stanford. "But others are confused. They have heard mixed messages and don't know what to do and are looking to the doctor for the final decision. And that's the problem with medicalization — it is essentially legitimizing the practice."

Modrek and her colleague, Maia Sieverding, PhD, social scientist in the global health sciences at the University of California-San Francisco, surveyed a group of mothers in the greater Cairo area in early 2014 and conducted in-depth interviews with 29 of them to discern their attitudes on female genital cutting. The results were published online Aug. 25 in *International Perspectives on Sexual and Reproductive Health.*

Effort to eradicate practice

Modrek said the practice, which is common in northern sub-Saharan Africa, is believed to have originated in Egypt's Nile Valley and goes back thousands of years to the time of the pharaohs. The procedure, typically done on girls between the ages of 7 and 14, involves cutting away a portion of the female genitals; in some countries, including Egypt, this involves removal of the clitoris, but in more extreme cases the entire external genitalia is removed. The procedure can lead to a wide range of medical problems, including severe pain and bleeding, infections, problems urinating, cysts, sexual problems, complications in childbirth and death, according to the World Health Organization.

More than 200 million women in 30 countries worldwide have undergone the procedure, according to the WHO, which has widely promoted abandonment of the practice, which it considers a violation of women's and girls' rights.

A 1994 United Nations International Conference on Population and Development in Egypt provoked national debate on the practice and sparked the growth of a women's movement to eradicate the procedure.

Since then, national media campaigns have drawn attention to the risks of female genital cutting, which was outlawed in 1997 unless "medically necessary." In 2007, the government closed this loophole in the law following outrage over the cutting-related death of an 11-year-old girl. More recently, in June of this year, a 17-year-old girl died of complications from the procedure, which was performed in a doctor's office, according to news reports.

These changes have led to a decline in the practice in Egypt. According to estimates from the 2014 Survey of Young People Egypt, there has been a 10 percent drop since 2002 in rates of female genital cutting among girls ages 13 to 17.

The roles of mothers

Modrek, a health economist, said she became interested in the issue while researching the effects of education on fertility among women in the Middle East. She began to notice the trends in Egypt on female genital cutting, in particular the move toward medicalization of the procedure. She and Sieverding, who lived in Cairo, became interested in how physicians were influencing women's decisions about female genital cutting — an issue that had been discussed but not systematically studied before, she said.

They identified 269 women living in an urban neighborhood near Cairo and another 141 in a semi-rural neighborhood outside the capital city. Some 68 percent were Muslim while the remaining participants were Christian, a religious minority in Egypt. Some 69 percent had completed at least secondary education, while 32 percent had only completed primary school or less.

The study focused on mothers, as they are the primary decision-makers when it comes to female genital cutting, though most also respect the opinions of their husbands and their own mothers, the researchers said. The average age of the participants was 31. Ninety-two percent of them had been circumcised themselves.

The women were asked to complete a detailed questionnaire about themselves and their attitudes toward the procedure, including questions about education, religion and health, and the role of female genital cutting in marriage, family and community life. Some then agreed to sit down for a more in-depth conversation, lasting up to an hour, to further probe their views on the highly sensitive topic. A local research associate conducted all the interviews, Modrek said.

Results showed that many women were seeking out doctors' opinions — typically a family doctor or gynecologist — because they were unsure whether the procedure was medically necessary and were looking for validation from an authoritative source. Muslim women were more likely to seek out doctors for advice, with 37 percent saying they would seek this counsel, while only 5 percent of Christian women said they would look to doctors for guidance.

Ambiguity from physicians

In the interviews, the mothers said they were conflicted — caught essentially between a longstanding cultural tradition and media messages indicating it could be harmful, Modrek said. Some expressed fear that their daughter would "hemorrhage and die" — language commonly used in media campaigns — and believed physicians would be better able to deal with these possible consequences, the researchers reported.

"The women said, 'I'm going to the doctor because I am hearing I shouldn't do this, but my mother says I should do it and my mother-in-law says I should do it. You, the doctor, are the expert. Do we need to do this to our daughter?'" Modrek said.

But the women said they received ambiguous messages from physicians, some of whom examined the girls and told them to come back another time. In nearly all cases, doctors did not explicitly reject the idea, but gave the women vague answers about the possible "need" for the procedure, the researchers reported.

"That's the slippery slope," Modrek said. "The doctor is seen as the more legitimizing voice and the voice of reason. Based on the women we interviewed, the doctors are not coming out and saying, 'You really don't need to do this.'"

As a next step, she said she hopes to do a study querying physicians directly on their attitudes and practices toward the procedure.

The study was funded by a seed grant from the Freeman Spogli Institute for International Studies at Stanford.

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

E-cigarette

continued from page 2

often patients thanked providers for their answers, they also spotted a trend: Most thanks were directed at doctors who had given a positive message about e-cigarettes.

"That finding is really interesting in thinking about how physicians might best connect with their patients," said Brown-Johnson. "Doctors might consider conveying their information about e-cigarettes in a nonjudgmental way, even when conveying the risks."

Educating doctors

The study also suggested other ways that scientists who research vaping and smoking might help doctors better communicate with their patients. "It showed us the need for provider education on e-cigarettes so they are aware of the limitations of what's known," said Prochaska. Future studies, they said, could inform how doctors may tailor messages on e-cigarettes to different types of patients.

Andrea Burbank, MD, the other co-lead author and a former Stanford Health4All fellow, said the research "is an example of evidence-based medicine in the information age. With this data we were able to rapidly prioritize real-world concerns about e-cigarettes for policymakers and researchers."

Other Stanford authors are former Stanford Health4All fellow Arianna Wassmann, MD; postdoctoral scholar Eric Daza, DrPh; and research assistant Amy Chieng.

Prochaska has provided expert witness testimony in litigation against tobacco companies and consults with Pfizer on smoking cessation medication. Wassmann was previously employed at HealthTap, which was founded by an alumnus of the Stanford Graduate School of Business, and holds stock options in the company.

MARC BRUXELLE / SHUTTERSTOCK.COM

Researchers analyzed an online medical forum to better understand what patients want to know about e-cigarettes and how doctors respond to questions about the devices.

The study was funded by the National Heart, Lung and Blood Institute and the State of California Tobacco-Related Disease Research Program.

The Stanford Department of Medicine also supported the work. **ISM**

Stanford's lab for cell, gene medicine opens in Palo Alto

NORBERT VON DER GROEBEN

The laboratory is Stanford's first dedicated facility to comply with the Food and Drug Administration's current good manufacturing practices.

By Krista Conger and Christopher Vaughan

Set back from the street, the building on California Avenue, in Palo Alto, looks like what you might see on Stanford's main quad — with pale, beige stucco walls, a series of arched windows framed by columns and a red tile roof. In a former life it was the Stanford Genome Technology Center; now it's found a new purpose as the Stanford Laboratory for Cell and Gene Medicine.

With clean rooms and all the regulatory clearances necessary to safely make cell-based therapies for use in human patients, the lab will create new opportunities for research and to facilitate advances in patient care.

The lab formally marked its opening with an open house on Sept. 6.

The laboratory is Stanford's first dedicated facility to comply with the Food and Drug Administration's current good manufacturing practices. These are standards the agency uses to ensure safety and consistency in medical therapies intended for use in humans.

The lab is devoted to making biological materials for use in phase-1 and phase-2 clinical trials. Until now, Stanford researchers wishing to conduct clinical trials of cells or viruses had to arrange to have them manufactured at other sites around the country.

'A vast pipeline'

"Stanford has a vast pipeline of potential cell and gene therapies that can now be realized without having to go off-site to make materials for testing," said laboratory director David DiGiusto, PhD. "Our hospital and clinics are world-renowned, and we've seen an explosion in cell therapy. We've built a biologics manufacturing facility to support the translation of cell and gene therapy from the research lab to the clinic. The LCGM expands our capacity more than twofold and will help researchers and clinicians test potential therapies safely and more rapidly."

"We test every product before it goes out the door."

These therapies include, among many others, purified blood stem cells to treat genetic diseases, immune cells engineered to attack cancers, and viruses equipped to replace faulty genes with healthy, functional copies in an attempt to treat conditions as diverse as severe combined immune deficiency, sickle cell anemia and a blistering skin disorder known as epidermolysis bullosa.

"The Laboratory for Cell and Gene Medicine is going to be a major force in our precision health revolution," said Lloyd Minor, MD, dean of the School of Medicine. "Our hope is that stem cell and gene-based therapeutics will enable Stanford Medicine to not just manage illness but cure it decisively and keep people healthy over a lifetime."

Maria Grazia Roncarolo, MD, a professor of pediatrics and of medicine and co-director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, helps to lead the school's efforts to translate basic scientific discoveries in the field of regenerative medicine into stem-cell and gene therapies. She said the new lab is an essential component of that effort.

"The LCGM will manufacture cell- and gene-based cures but also develop innovative technologies to make these therapies more accessible and available to all patients in need," she said.

The lab is being funded by the School of Medicine, Stanford Health Care and Stanford Children's Health.

The roughly 25,000-square-foot building has been completely remodeled to include clean rooms with airlocks, poured floors that don't have cracks that can harbor bacteria, and easily sanitized surfaces. It includes separate areas for cell processing and for the development of viral vectors designed to infiltrate human cells.

"Most of our rooms undergo 40 to 60 full changes of filtered air per hour, which is like turning over the whole volume of a room every minute," said DiGiusto. "We use special, breathable culture bags rather than tissue culture flasks to grow cells, and we transfer liquids with pharmacy pumps rather than pipettes. Everything we do is conducted according to strict, written procedures."

Stringent practices

Current good manufacturing practices require a high degree of sterility, strict chain-of-custody protocol and practices to ensure consistency in products. One focus of the facility will be the generation of banks of induced pluripotent stem cells and other specialized tissues such as heart muscle cells, that are derived from stem cells. These cells can be used to test the effects of drugs in a "clinical trial in a dish" or potentially even used to repair tissues injured by disease or trauma.

"We test every product before it goes out the door," said DiGiusto, who is also the director of stem cells and therapeutic operations at the laboratory. Other directors will oversee quality assurance, regulatory affairs and other aspects of the laboratory's operations. "We have a high degree of control over all stages of manufacture, and every stage is documented according to federal law."

In addition to manufacturing biological products, the laboratory will also serve as a kind of pharmacy to dispense cellular therapies that were made in other facilities compliant with current good manufacturing practices. These therapies will be for Stanford patients, as well as for patients at collaborating institutions. "Unlike a typical pharmacy, we will wash, store and distribute cells, rather than drugs," said DiGiusto. "This will ensure each patient receives the right product at the right dose and at the right time."

Plans are also in place to support collaborations among researchers from Stanford and elsewhere. DiGiusto and his colleagues are working to be licensed by the state of California as a biological manufacturer so that materials made in the laboratory can be shipped across state lines. They will also file a facility master file with the FDA so that non-Stanford collaborators can receive approval to use the laboratory.

In the end, the lab's activities will be driven by the needs of the Stanford community, DiGiusto said.

"This is very much a partnership with the faculty of the medical school," he said. "We will have a formal process for project management and budgeting, and we are here to help them develop clinical trials. But the ideas of what to produce will come from them." **ISM**

NORBERT VON DER GROEBEN

NORBERT VON DER GROEBEN

David DiGiusto (top) is director of the Stanford Laboratory for Cell and Gene Medicine. Bryan Fox (bottom) is a senior scientist there.

Common mechanism of Parkinson's disease pathology discovered

By Bruce Goldman

School of Medicine researchers have located an intracellular defect that they believe is probably common to all forms of Parkinson's disease.

This defect, which precedes the death of a group of nerve cells whose loss is the hallmark of the condition, play a critical role in triggering that die-off.

"We've found a molecular biomarker that characterizes not just familial cases of Parkinson's, in which a predisposition for the disease is clearly inherited, but also the condition's far more prevalent sporadic forms, for which the genetic contribution is either nonexistent or not yet discovered," said Xinnan Wang, MD, PhD, assistant professor of neurosurgery.

The defect, described in a study published online Sept. 8 in *Cell Stem Cell*, renders cells unable to quickly dismantle their internal power packs, called mitochondria, when they wear out, stop supplying energy and start spewing out pollutants instead. This discovery could lead to not only more accurate but much earlier diagnoses of Parkinson's disease and could also point to entirely new pharmacological approaches to treating it, said Wang, who is the study's senior author. The lead author is postdoctoral scholar Chung-Han Hsieh, PhD.

The second-leading neurodegenerative disorder after Alzheimer's disease, Parkinson's affects one in every 60-70 Americans age 65 or older. While 5-10 percent of all cases are familial, the vast majority are sporadic.

Prevalent mutation in Parkinson's

The most frequent genetic mutations responsible for familial Parkinson's occur at various points along a gene coding for a protein called LRRK2. Several such mutations are known, but genetic tests reveal that the mutation known as LRRK2G2019S is the most prevalent, turning up in 1 in 20 familial cases and 1 in every 50 apparently sporadic cases among Caucasians. Curiously, LRRK2G2019S shows up in 40 percent of familial Parkinson's cases and 13 percent of sporadic cases among Ashkenazi Jews; figures for North African Berbers are 39 and 40 percent, respectively.

Until now, no one could clearly account for LRRK2's connection to Parkinson's. In an extensive series of experiments with cells cultured from Parkinson's patients and healthy subjects, Wang and her colleagues have cleared up that mystery.

Mitochondria convert fats and sugars into other molecules that transport energy where it's needed in a cell. A single nerve cell can host hundreds or even thousands of mitochondria. A vast supply of energy is particularly crucial for a group of midbrain nerve cells whose nonstop activity fine-tunes our voluntary movements: These cells constantly produce and secrete a substance called dopamine (they're called "dopaminergic"), and each sends out numerous long-distance, dopamine-squirting cellular extensions to elsewhere in the brain. The failure of these dopamine-producing midbrain nerve cells triggers the classic symptoms of Parkinson's disease: tremor, stiffness, difficulty initiating and sustaining voluntary motion, and, sometimes, cognitive difficulties.

Until now, the question of what causes the death of these dopaminergic nerve cells in Parkinson's patients has occasioned many highly uncertain guesses backed by little solid evidence. This uncertainty limits medical practitioners' ability to diagnose Parkinson's early on, and it impedes drug developers' attempts to find effective treatments.

Malfunctioning mitochondria are like old jalopies: Their fuel efficiency is rotten, and they spew out tons of toxic exhaust in the form of corrosive chemicals called free radicals. But, the Stanford scientists showed, before faulty mitochondria can be decommissioned, they must first be detached from the cytoskeleton, a network of molecular filaments and tubules that spans and shapes most of our cells. Only after the mitochondria are detached can the cell destroy them. But this can't happen, Wang's team found, until a protein called Miro that anchors mitochondria to the cytoskeleton is severed.

Removing Miro

The researchers discovered that Miro's removal can occur only after LRRK2 forms a complex with Miro. Defective LRRK2 is impaired in forming this complex, resulting in significant delays in Miro's removal.

In the study, Wang and her associates obtained 20 different lines of cultured fibroblasts from human skin: four from healthy subjects; five from apparently sporadic Parkinson's patients; six from familial patients with LRRK2 mutations, including the notorious LRRK2G2019S; and five from familial patients with other mutations.

Six hours after biochemically inducing mitochondrial damage in these cells, the scientists broke open some of them to observe signs of Miro degradation. At 14 hours post-biochemical assault, they broke more cells open to monitor mitochondrial breakdown. In all four cultured fibroblast lines from healthy subjects, that's just what they witnessed. But to their surprise, mitochondrial detachment and breakdown were substantially delayed in all 16 cell lines representing Parkinson's cases.

Digging deeper, the scientists used advanced methods to create nerve cells enriched for dopaminergic activity from several of the skin-fibroblast lines.

"Medicines that lower Miro levels could prove beneficial in treating the disease."

They then employed techniques ranging from live imaging with microscopic cameras to biochemical manipulations to show that damaged mitochondria in the dopaminergic nerve cells generated from healthy subjects' fibroblasts quickly led to those mitochondria being destroyed. But in the dopaminergic nerve cells derived from the cells of patients with LRRK2G2019S-mutant Parkinson's, this process and the key steps leading up to it were substantially delayed.

Free radicals

When the researchers biochemically induced excessive free-radical production in the nerve cells, those from every Parkinson's patient sampled — familial and sporadic alike — died in much greater numbers than equivalent cells derived from healthy patients.

"The healthy cells could handle higher free-radical concentrations," Wang said. "But the Parkinson's cells were more prone to dying under those conditions, which are apt to occur in the energy-intensive, mid-brain, dopamine-producing nerve cells that degenerate in Parkinson's disease."

Remarkably, the scientists discovered they could prevent the delay in Parkinson's-derived nerve cells' dismantling of faulty mitochondria, as well as forestall those cells' untimely death in the face of free-radical onslaught. They performed a biochemical trick that reduced Miro levels in the cells. The reduction wasn't enough to dislodge healthy mitochondria from the cytoskeleton, but it reduced their attachment intensities closer to the point at which detachment could occur. When the scientists then chemically induced mitochondrial damage, no increased mitochondrial drop-off or degradation took place in the nerve cells derived from healthy subjects. But in the equivalent LRRK2G2019S nerve cells, the previously seen delays pretty much disappeared — and far fewer of these cells died. Lowering Miro concentrations, in those cells, compensated for their Miro-chopping impairment.

In a fruit-fly model of LRRK2 linked-Parkinson's locomotion difficulties (good rodent models for this aspect of Parkinson's don't exist), lowering Miro levels resulted in the restoration of larvae's visibly compromised crawling ability and fully reversed deficits in the climbing and jumping abilities of adult flies.

Wang's team also proved that LRRK2 is recruited to sites of mitochondrial stress. They believe many different intracellular difficulties can contribute to the failure of even a perfectly normal LRRK2 complex with Miro, and that Miro's resultant failure to release its grip may be a reliable early biomarker — and possibly the crucial causal event — of Parkinson's disease.

"Existing drugs for Parkinson's largely work by supplying precursors that faltering dopaminergic nerve cells can easily convert to dopamine," Wang said. "But that doesn't prevent those cells from dying, and once they've died you can't bring them back. Measuring Miro levels in skin fibroblasts from people at risk of Parkinson's might someday prove beneficial in getting an accurate, early diagnosis. And medicines that lower Miro levels could prove beneficial in treating the disease."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

NORBERT VON DER GROEBEN

Xinnan Wang said the discovery could lead to more accurate and much earlier diagnoses of Parkinson's disease, as well as point to entirely new pharmacological approaches to treating it.

Additional Stanford authors are Theo Palmer, PhD, associate professor of neurosurgery; basic life science research associate Atossa Shaltouki, PhD; graduate student Ashley Gonzalez; postdoctoral scholar Alexandre Bettencourt da Cruz, PhD; and former life science research associate Erica St. Lawrence.

The study was funded by the National Institutes of Health, the William N. and Bernice E. Bumpus Foundation, the Alfred P. Sloan Foundation, the Klingenstein Foundation, the Shurl and Kay Curci Foundation, the California Institute of Regenerative Medicine, the Michael J. Fox Foundation for Parkinson's Research and the Blume Foundation.

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

Three researchers receive grants for study of pediatric cancer

Three Stanford researchers have received grants from the St. Baldrick's Foundation to study pediatric cancer.

Kara Davis, DO, instructor of pediatrics, was awarded $115,000 to study the differences between acute lymphoblastic leukemia cells and normal developing blood cells. The study will combine single-cell measurements of childhood leukemia samples and healthy bone marrow with machine-learning techniques to identify cells associated with relapse at the time of diagnosis.

Melissa Mavers, MD, PhD, a Tashia and John Morgridge Endowed Postdoctoral Fellow in Pediatric Translational Medicine, was awarded $195,000 from the foundation's Rays of Hope Hero Fund to study methods to improve stem cell transplantation so that the likelihood of graft-versus-host disease is reduced while maintaining graft-versus-leukemia effect.

Liora Schultz, MD, instructor of pediatrics, was awarded $330,000 to develop targeted methods to disrupt inhibition of anti-tumor immune cells. **ISM**

Anatomy

continued from page 1

ROD SEARCEY

four other teammates took their turns.

"How deep should we go?" Brewster asked, looking up at the team's teaching assistant, Heather desJardins-Park, a second-year medical student. Cut through the skin to the subcutaneous fat, then down through the deep fascia — the connective tissue — to the chest muscle, the pectoralis major, she told them. Then stop. Don't cut too deep, she added.

As the students made the first slices into skin, their tense faces relaxed and the learning began. A faint odor of formaldehyde hung in the air. The team members at table 3 took a moment to discuss their feelings about cutting into a cadaver, how they thought they should feel, how they actually felt. Contreras wanted to see the cadaver's face so that he could feel more like he was working with an actual person. The cadavers' heads will remain covered with gauze throughout the first quarter. The students see only the outlines of the lips, the profile of a nose.

'Respect and care'

"Every now and then it hits me this is a real person," Contreras said. "But with the face not visible, it seems less sacred."

"I feel like if I saw the face, my hands would be shaky," said Tim Chai, an MD-PhD student and UCLA graduate, looking down at his gloved hands.

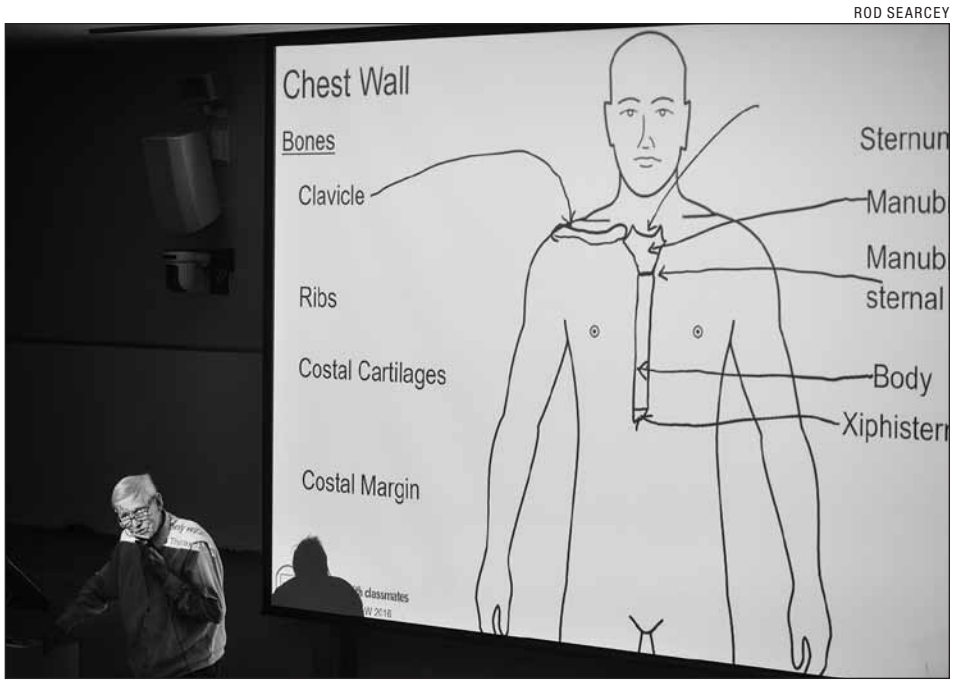
"This is, like, us," Brewster said with amazement, glancing inside the chest of the cadaver, meaning this was a glimpse inside what their own bodies actually look like.

Team 3's cadaver is a male. The five students will learn his age and cause of death in the coming days. In the second quarter, after the head is uncovered, they will dissect the head and neck. In March, after completion of the course, the class will hold a ceremony to honor their cadavers. They can write thank-you notes to the families of the donors if they choose, but they will not be told their cadavers' names or the names of their family members.

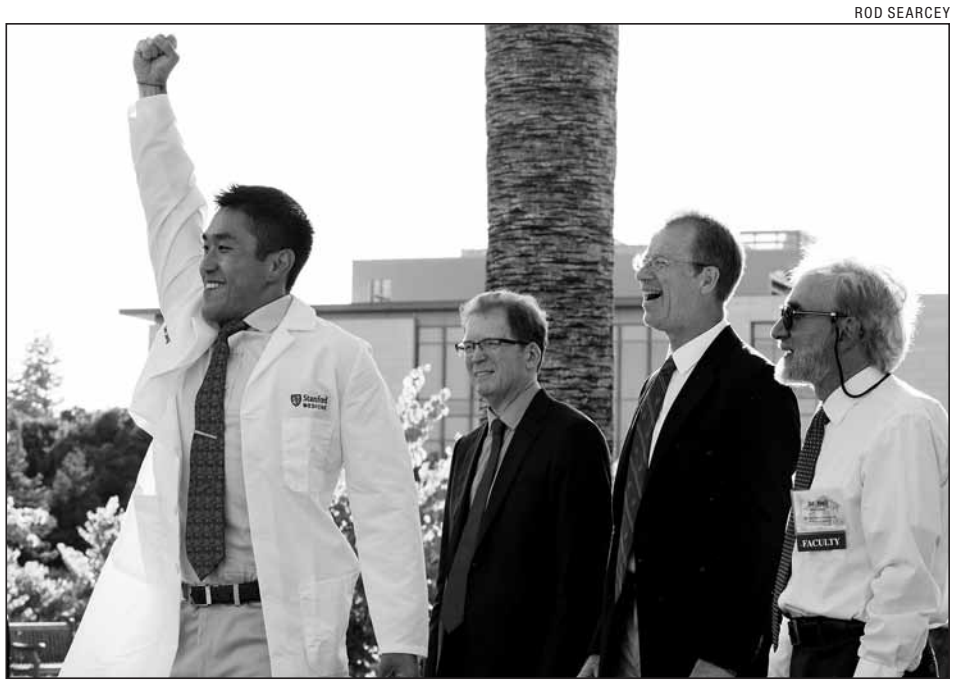
"At the end of the day, medicine is all about the patient," Srivastava said. "The patient should be the center of the universe. We keep the cadaver at the center of this course. It encourages students to think about bodies as human. It teaches empathy.

"We treat our cadavers as we would treat our patients: with respect and care." **ISM**

ROD SEARCEY



ROD SEARCEY



Maria Interrante (top) listens to the Clinical Anatomy lecture Aug. 30 before heading to the anatomy lab. John Gosling (bottom) is an instructor in the course.

New medical student Sam Jiang shows some enthusiasm after receiving his white coat in a ceremony Aug. 26.

Retinoic acid

continued from page 1

years to be involved in suppressing inflammation in the intestine. We wanted to connect the dots and learn whether and how retinoic acid levels directly affect cancer development."

Engleman is the senior author of the research, which was published online Aug. 30 in *Immunity*. Postdoctoral scholar Nupur Bhattacharya, PhD, and graduate student Robert Yuan share lead authorship of the study.

Tumors in mice

Retinoic acid is essential for many processes of growth and development, but it also degrades quickly when exposed to light. This makes it extremely difficult to accurately detect levels of the metabolite in the body.

The Stanford researchers collaborated with colleagues at the University of California-Berkeley, who devised a way to use a technique called quantitative mass spectrometry to measure the retinoic acid in intestinal tissues of mice treated with one or both of two chemicals: a chemical that causes intestinal inflammation, and a chemical that stimulates the development of colorectal cancer. Mice who received both chemicals develop intestinal tumors within nine to 10 weeks of treatment; those treated with just the first chemical develop intestinal inflammation but not cancers.

Engleman and his colleagues found that the mice that developed colorectal cancer had significantly lower-than-normal levels of retinoic acid in their gut than those whose intestines were inflamed but not cancerous. Further investigation showed the intestinal tissue of the animals with cancer made less of a protein that synthesizes retinoic acid and about four times more of a protein that degrades retinoic acid, leading to a rapid net decrease in levels of the metabolite.

Restoring retinoic acid levels

The researchers then tested whether it was possible to affect the disease progression by bringing the levels of retinoic acid in the tissue back into a more normal range.

"When we increased the amount of retinoic acid in the intestine, either by supplementing the animal with retinoic acid or by blocking the activity of the degradation enzyme, we were able to dramatically reduce the tumor burden in the animals," said Engleman. "Conversely, inhibiting retinoic acid activity significantly increased the tumor burden."

The researchers next investigated the levels of the synthesis and degradation proteins in stored samples of intestinal tissue obtained from people with either ulcerative colitis or colorectal cancer associated with ulcerative colitis. Because the samples had been stored, rather than freshly collected, it was not possible to directly measure the retinoic acid levels in the human tissues.

> "Inhibiting retinoic acid activity significantly increased the tumor burden."

The researchers found that, similar to what they had seen in the mice, human colorectal cancer tissue had higher levels of the degradation protein and lower levels of the synthesis protein than were found in tissue that was simply inflamed. Furthermore, they saw an inverse correlation in the amount of degradation protein and how long the patient had lived. In other words, those patients with increased amounts of the degradation enzyme in their intestinal tissue tended to fare more poorly than others with less of the enzyme.

STEVE FISCH

Edgar Engleman is senior author of a study that found that levels of retinoic acid are low in mice and humans with colorectal cancer.

Because the researchers also observed similar changes in protein levels in tissue samples from patients with colorectal cancer but with no prior history of ulcerative colitis, they wondered if there could be another cause of intestinal inflammation that affects retinoic acid levels. They knew that naturally occurring bacteria in the gut can sometimes cause local inflammation and hypothesized that they might contribute to the development of retinoic acid deficiency and colorectal cancer. Depleting these bacteria by treating mice with broad-spectrum antibiotics dramatically reduced tumor formation in several colorectal cancer models and prevented the alteration in retinoic acid metabolism that was seen in mice with colorectal cancer and in the human intestinal tissue.

"We found that bacteria, or molecules produced by bacteria, can cause a massive inflammatory reaction in the gut that directly affects retinoic acid metabolism," said Engleman. "Normally retinoic acid levels are regulated extremely tightly. This discovery could have important implications for the treatment of human colorectal cancer."

Further investigation showed that retinoic acid blocks or slows cancer development by activating a type of immune cell called a CD8 T cell. These T cells then kill off the cancer cells. In mice, lower levels of retinoic acid led to reduced numbers and activation of CD8 T cells in the intestinal tissue and increased the animals' tumor burden, the researchers found.

"It's become very clear through many studies that chronic, smoldering inflammation is a very important risk factor for many types of cancer," said Engleman. "Now that we've shown a role for retinoic acid deficiency in colorectal cancer, we'd like to identify the specific microorganisms that initiate these changes in humans. Ultimately we hope to determine whether our findings could be useful for the prevention or treatment of colorectal cancer."

Other Stanford co-authors of the work are graduate student Tyler Prestwood; former clinical fellow Michael DiMaio, MD; postdoctoral scholars Nathan Retticker-Flynn, PhD, Justin Kenkel, PhD, Yaron Carmi, PhD, and Hweixian Leong Penny, PhD; clinical assistant professor of pathology Tho Pham, MD; lab manager Lorna Tolentino; research assistant Okmi Choi; and undergraduate student Reyna Hulett.

The research was supported by the National Institutes of Health.

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

Sleep

continued from page 1

is the senior author. The lead author is postdoctoral scholar Ada Eban-Rothschild, PhD.

"This has potential huge clinical relevance," de Lecea said. "Insomnia, a multibillion-dollar market for pharmaceutical companies, has traditionally been treated with drugs such as benzodiazepines that nonspecifically shut down the entire brain. Now we see the possibility of developing therapies that, by narrowly targeting this newly identified circuit, could induce much higher-quality sleep."

Some 25 to 30 percent of American adults are affected by sleep disturbances of one type or another, according to the National Institutes of Health. In addition, disruption of the sleep-wake rhythm typifies many different neuropsychiatric disorders and is understood to exacerbate them.

One of the first questions a psychiatrist asks a patient, said de Lecea, is, "How's your sleep?"

Similarity across vertebrates

The reward system's circuitry is similar in all vertebrates, from fish, frogs and falcons to fishermen and fashion models. A chemical called dopamine plays a crucial role in firing up this circuitry.

Neuroscientists know that a particular brain structure, the ventral tegmental area, or VTA, is the origin of numerous dopamine-secreting nerve fibers that run in discrete tracts to many different parts of the brain. A plurality of these fibers go to the nucleus accumbens, a forebrain structure particularly implicated in generating feelings of pleasure in anticipation of, or response to, obtaining a desired objective.

"Since many reward-circuit-activating drugs such as amphetamines that work by stimulating dopamine secretion also keep users awake, it's natural to ask if dopamine plays a key role in the sleep-wake cycle as well as in reward," Eban-Rothschild said. "But, in part due to existing technical limitations, earlier experimental literature has unearthed little evidence for the connection and, in fact, has suggested that this circuit probably wasn't so important."

For the new study, the investigators employed male laboratory mice bioengineered in several respects to enable the use of advanced technologies to remotely excite, suppress and monitor activity in the dopamine-secreting nerve cells from the mice's VTA. They also measured the mice's overall brain activity and muscle tone to determine the mice's relative stages of asleep or arousal. The researchers used video cameras to view the mice's behavior.

Observed in mice

Overall, activity in the dopamine-secreting nerve cells emanating from the VTA rose on waking and stayed elevated when mice were awake. Conversely, this activity ramped down when mice transitioned into sleep, remaining low while they slumbered. Activating this nerve-cell population was enough to rouse the animals from a sound sleep and keep them awake for long periods, even during a point in the mice's diurnal cycle when they'd ordinarily be bunking down. Control animals, whose VTA activity wasn't similarly jacked up, built little nests from pellets of materials placed in all the mice's cages and promptly dropped off.

When instead the scientists suppressed activity in the same nerve-cell population during the typically active period of the mice's 24-hour cycle, the mice conked out, snoozing through the presence of surefire arousal triggers: delicious high-fat chow, a female or fear-inducing fox urine.

Mice in an unfamiliar cage ordinarily explore their new surroundings energetically. And indeed, VTA-suppressed mice stayed awake for the first 45 minutes of the hour they spent in a new cage. But Eban-Rothschild noticed something: They spent that waking time building nests.

"They were really careful about it," she noted. Once they were satisfied with what they'd built, they dozed off.

This wasn't just some stereotyped behavior guaranteed to emerge when VTA activity was inhibited, Eban-Rothschild added. "If we put the nest they'd already built in their usual cage into the novel cage, they climbed in and went right to sleep."

Control mice in the unfamiliar cage ran around, either ignoring the pellet of nesting materials placed inside or scattering those materials all over the cage.

Nest-making activities

Eban-Rothschild analyzed video footage of the animals' behavior in their novel environments, and correlated 1-second video segments with recorded brain activity during the corresponding time frame. She saw that actions directly connected to building nests were marked by reduced VTA activity, while actions that weren't were associated with higher levels of VTA activity.

"We knew stimulating the brain's dopamine-related circuitry would increase goal-directed behaviors such as food- and sex-seeking" said Eban-Rothschild. "But the new study shows that at least one complex behavior is induced not by stimulating, but by inhibiting, this very circuit. Interestingly, this behavior — nest building — is essential to a mouse's preparation for sleep."

Nobody had noticed that before, said de Lecea. "This is the first finding of a sleep-preparation starter site in the brain. It's likely we humans have one, too. If we're disrupting this preparation by, say, reading email or playing videogames, which not only give off light but charge up our emotions and get our VTA dopaminergic circuitry going, it's easy to see why we're likely to have trouble falling asleep."

Noting that this anticipatory phase is often at the root of many people's sleeping problems, de Lecea suggested that the newly identified circuit could be a target for pharmacological intervention to help people ease into sleep.

"We have plenty of drugs that counter dopamine," he said. "Perhaps giving a person the right dose, at just the right time, of a drug with just the right pharmacokinetic properties so its effect will wear off at the right time would work a lot better than bombarding the brain with benzodiazepines, such as Valium, that knock out the entire brain."

He said he also sees the possibility that drugs targeting the VTA's dopamine-secreting nerve cells could benefit those suffering from neurological conditions such as schizophrenia or bipolar disorder that are characterized by sleep-wake cycle disturbances.

"It could be that merely solving the sleep-wake part will clear up a lot of symptoms," de Lecea said.

Other Stanford co-authors of the study are postdoctoral scholar William Giardino, PhD, and former postdoctoral scholar Jeff Jones, PhD.

The study was funded by the National Institutes of Health, the Brain and Behavior Research Foundation, the U.S. Israel Binational Science Foundation, the Klarman Family Foundation and the Edmond and Lily Safra Center of Brain Science.

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

NORBERT VON DER GROEBEN

Luis de Lecea says the discovery about the brain circuit's role in the sleep-wake cycle could point the way toward developing therapies for sleep disorders that target specific parts of the brain.

Patients newly diagnosed with breast cancer sought for study about treatment decisions

By Tracie White

The School of Medicine is recruiting women who have been newly diagnosed with breast cancer for a clinical study examining the various factors that influence how women make treatment decisions during this stressful time.

"We would like to better understand how women think and feel as they are deciding on which cancer treatment options are best for them, including the possibility of having surgery to remove both the affected and the unaffected breast," said Bita Nouriani, MS, clinical research manager for the trial. "The results of this five-year study will help determine what kinds of support would best assist women newly diagnosed with breast cancer to make these difficult treatment decisions."

The principal investigators are David Spiegel, MD, professor of psychiatry and behavioral sciences and director of the Stanford Center on Stress and Health; Amit Etkin, MD, PhD, associate professor of psychiatry and behavioral sciences; James Gross, PhD, professor of psychology; and Allison Kurian, MD, MS, associate professor of oncology.

The study is designed to collect neurophysiological and psychological information from women who are suddenly faced with a breast cancer diagnosis and many treatment decisions.

"Women diagnosed with breast cancer face difficult treatment choices within a limited amount of time," Nouriani said. Treatment options range from surgery, radiation therapy, chemotherapy, hormone therapy, targeted drug therapy or some combination of these.

Women who want to participate in the study will be asked to undergo assessments that include questionnaires, brain MRI testing and saliva sample collection.

"The functional MRI assessment will measure emotional reactions to the stress of the cancer diagnosis and the need to make treatment choices, and the saliva sample will be used to measure levels of cortisol, a stress hormone," Spiegel said. "We will follow up with questionnaires to see how participants are doing six, 12 and 18 months later."

The researchers plan to recruit 130 women diagnosed with breast cancer and 40 healthy women for comparison. All must live in the San Francisco Bay Area. Each will receive as much as $550 for completing study participation. The study is sponsored by the National Cancer Institute.

Patients interested in participating are encouraged to contact Nouriani at 723-5736 or by email at treatment-decisionstudy@stanford.edu. **ISM**

Jonathan J. King Lecture to focus on dealing with conflicts over care

Patient-communication and palliative-care expert Robert Arnold, MD, will deliver the 26th annual Jonathan J. King Lecture at 5:30 p.m. Sept. 27 at the Li Ka Shing Center for Learning and Knowledge.

Arnold's lecture, titled "Dealing With Conflict Over 'Appropriate Care': How Can Clinicians Do Better," is free and open to the public.

The Leo H. Creip Chair of Patient Care and a professor of internal medicine at the University of Pittsburgh, Arnold conducts research and develops curricula on improving how doctors communicate with patients who have life-limiting illnesses, and also examines how medical-ethics principles are incorporated into clinical practice. He serves as medical director of the University of Pittsburgh Medical Center Palliative and Supportive Institute and is clinically active in palliative care.

The endowed lectureship was established in 1991 to bring attention to the importance of compassionate and humane care for all patients. It honors Jonathan King, who earned a master's degree and PhD in computer science at Stanford and who became an advocate for patients' rights after his diagnosis of cancer in 1989.

The Center for Biomedical Ethics organizes the annual event. **ISM**

Project to enroll thousands to explore wellness in U.S., China, Taiwan

By Jennie Dusheck

The Stanford Prevention Research Center launched a clinical research project today to enroll thousands of people in California, China and Taiwan in a study exploring wellness and the connection between a sense of well-being and physical health.

The project, the Wellness Living Laboratory, will collect a variety of health data from participants who, in return, can learn more about well-being and try interventions intended to enhance wellness.

Instead of studying the causes and consequences of disease, WELL will emphasize research on overall health. Its ultimate goal is to improve the health and well-being of whole populations by identifying what factors help people maintain health and wellness and by developing techniques that help people behave in ways that are healthful.

"It's an effort to change the world of medicine and health," said John Ioannidis, MD, DSc, professor of medicine and director of the Stanford Prevention Research Center. "It may sound very ambitious, but I see this as a way to refocus the key priorities of biomedical research."

WELL has established partnerships with researchers and public health departments in the nine-county San Francisco Bay Area; New Taipei City, Taiwan; and Hangzhou, China, to measure well-being and health among residents in those areas.

Observational and interventionist

WELL is both an observational study and an interventional study. It aims to enroll at least 10,000 participants from each of the three sites. Researchers will collect health and wellness data and test behavioral modifications and other interventions that help people improve their health and wellness. Such interventions might include improving social, neighborhood and policy environments to support health and wellness, as well as finding ways to encourage people to quit smoking, eat better or exercise more.

WELL is a way for ordinary people to contribute to medical science and to eventually create healthier environments for their families and communities, said WELL director Sandra Winter, PhD, MHA. Participants can suggest topics that the team of researchers can include in their surveys. For example, in a soft launch in the Bay Area this summer, some of the 300 participants suggested that WELL study whether pet ownership affects wellness.

CHRISTOPHER SILAS NEAL

WELL is also considering survey modules on technology use, gut health, cognitive function, intimate relationships and major life events.

Looking at the big picture

Initial funding for the first five years was given to Stanford University through a $10 million gift from the Amway Nutrilite Health Institute Wellness Fund.

Winter and Ioannidis seek to steer biomedical research in a new direction, one that is more focused on prevention. "The vast majority of biomedical research has focused on treating diseases," said Ioannidis, "while a much smaller part has focused on maintaining health and maybe some prevention efforts. There's very, very little research that has tried to look at the big picture — what makes people happy, resilient, creative, fully exploring their potential and living not only healthy, but more-than-healthy, lives."

"This is not just about whether you're being physically active or eating and sleeping well," said Winter, "but about how your well-being affects your ability to engage in physical activity and how those activities, in turn, affect your well-being."

In the Bay Area, participants will respond to online surveys that evaluate health and well-being. Anyone 18 or older and living in the Bay Area's nine counties is invited to register at http://med.stanford.edu/wellforlife.html. For now, the surveys are in English only, but they will eventually be offered in Mandarin, Cantonese and Spanish.

In Hangzhou, participants ages 18 to 80 will be recruited over five years. The first 3,000 will be randomly selected from the 640,000 residents of the Xi'hu (West Lake) District and invited to join the study. Friends and relatives of the first group will then bolster the cohort. Researchers will evaluate them in person through surveys, biological specimens and eye exams.

In Taiwan, WELL will collaborate with the Taiwan Biobank, an initiative of the government there that aims to recruit 200,000 individuals for biomedical research. In addition to filling out the wellness-related surveys, participants in Taiwan will donate biospecimens, such as blood, stool, saliva and urine samples, to help identify the biomarkers of wellness.

More information about WELL is available in the summer issue of *Stanford Medicine*. Preliminary work in the Bay Area suggests that the components of well-being are complex and not always intuitive. For example, while a social network is important to a sense of well-being, difficult friends and family may also undermine well-being. And, likewise, ill health can lead many to re-evaluate their lives in ways that actually enhance a sense of well-being. **ISM**

OF NOTE

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

James K. Chen

Michael Fischbein

Jeffrey Goldberg

Andrew Huberman

Corey Keller

Matthew Lungren

Paul Maggio

Denise Monack

Jennifer Raymond

Sandhya Srinivas

JAMES K. CHEN, PhD, was promoted to professor of chemical and systems biology and of developmental biology, effective June 1. In his research, he examines the genetic and chemical regulators of the Hedgehog signaling pathway, develops optochemical tools to study organismal biology and uses zebrafish models to understand vertebrate development and tissue regeneration.

MICHAEL FISCHBEIN, MD, PhD, was promoted to associate professor of cardiothoracic surgery, effective March 1. He is the director of thoracic aortic surgery. His research focuses on the molecular and genetic mechanisms that lead to aortic aneurysms and on aneurysm formation in Marfan syndrome.

JEFFREY GOLDBERG, MD, PhD; **ANDREW HUBERMAN**, PhD; and researchers from several other institutions have received a three-year, $2.5 million grant as part of the National Institutes of Health's National Eye Institute Audacious Goals Initiative. The grants are intended to support projects that work to restore vision by regenerating neurons and their linkages within the eye and the brain. Goldberg is professor and chair of ophthalmology, and Huberman is associate professor of neurobiology. Their research project aims to identify genes and proteins that affect the ability of retinal ganglion cell axons to regenerate and function in mice.

MICKEY HU, PhD, associate professor of obstetrics and gynecology, received a $300,000 grant from AVON 39 The Walk to End Breast Cancer to investigate the effects of new drugs on cancer-related genes in metastatic breast cancer cells.

COREY KELLER, MD, PhD, a resident and a postdoctoral scholar in psychiatry and behavioral sciences, has received a 2016 Alpha Omega Alpha Postgraduate Research Award. The $2,000 prize will help support his work on the induction and quantification of long-term plasticity in the brain.

MATTHEW LUNGREN, MD, assistant professor of radiology, was named a 2016 GE Radiology Research Academic Fellow by the Association of University Radiologists. The program was created to foster original clinical and health-services radiology research. During his two-year fellowship, Lungren will investigate machine-learning techniques to support clinical decision-making in pediatric imaging.

PAUL MAGGIO, MD, was promoted to associate professor of surgery, effective March 1. He is associate chief medical officer, associate trauma medical director, co-director of critical care medicine and a medical director of informatics at Stanford Health Care.

DENISE MONACK, PhD, was promoted to professor of microbiology and immunology, effective June 1. Her research focuses on immune detection of intracellular bacterial pathogens and on chronic *Salmonella* infections, with an emphasis on the interactions between the bacteria and the immune system and between the bacteria and gut microbiota.

Creed Stary

Anand Veeravagu

JENNIFER RAYMOND, PhD, was promoted to professor of neurobiology, effective Jan. 1.

SANDHYA SRINIVAS, MD, was promoted to professor of medicine, effective July 1. She specializes in urologic oncology, and her research focuses on investigating new therapies for renal, prostate and other types of cancer.

CREED STARY, MD, PhD, was appointed assistant professor of anesthesiology, perioperative and pain medicine, effective July 1. His research focuses on the role of microRNAs and glia in promoting neuronal survival and improving mitochondrial function following ischemic brain injury.

ANAND VEERAVAGU, MD, was appointed assistant professor of neurosurgery, effective July 1. He is the director of minimally invasive neurospine surgery at Stanford Health Care. His research focuses on using large national databases to assess the cost, quality and effectiveness of various treatment algorithms and on predictive analytics. **ISM**