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 205, 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 Sakri 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.

By Krista Conger

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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 critical role in suppressing 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 years to suppress the growth of colorectal cancer in animals, but the mechanism by which it works in humans has been unknown.”

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 had been pinpointed, said Luis de Lecea, PhD, professor of psychiatry and behavioral sciences. The researchers’ findings were published online Sept. 5 in Nature Neuroscience.

By Bruce Goldman

Researchers found that when a brain circuit in mice was suppressed, they built nests and went to sleep.
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 patient 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, and few patients recover. The search for second 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, Neya Marina, MD, professor of pediatrics at the School of Medicine.

The rarity of osteosarcoma meant that a large, international collaboration was needed to enroll enough patients for a rigorous comparison of the two drug regimens. Doctors at Lucile Packard Children’s Hospital Stanford, and Marina is a pediatrician, 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 bone 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

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 radiation. The patients were then randomized to MAPIE or a standard MAP regimen.

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 carefully tracked. MAPIE did not lengthen event-free survival and caused more side effects than MAP.

“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 a second malignancy.” The study suggests that adding MAPIE 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.

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:

“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 often more than patients, with an expressed concern about addiction.

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

"The existence of smoking and waxing months of interactions with patients' questions...”
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.

“We found that it’s true some women were planning to do it [cut] anyway and are just going to the doctor’s office, according to news reports. "The women said, 'I'm going to the doctor because the hospital told me to,'” 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 procedure.”

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 Journal of 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 entire external genitalia. The procedure can lead to a wide range of medical problems, including severe pain and bleeding, infections, problems urinating, 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 Cairo, 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 under “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 a survey of 4,657 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 how physicians were influencing physicians’ decisions about female genital cutting — an issue that had been discussed but not systematically studied before, she said.

They identified 209 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 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.

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 complications. 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-law says I shouldn’t do it. You, the doctor, are the expert. Do we need to do this to our daughter?’”

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 not as the the clear 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.

E-cigarette continued from page 2

often patients thanked physicians for their answers, they also spotted a trend: 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.

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

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 logistics 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.”

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 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 air-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.”

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September 12, 2016
Inside Stanford Medicine
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.

Wang’s team found that a protein called Miro that attaches to mitochondria to the cytoskeleton is severed. This began a biochemical trick that Wang and her colleagues developed in a study published online Sept. 8 in Cell Stem Cell, renders cells unable to quickly dismantle their internal power packs, called mitochondria, which are apt to occur in the energy-intensive, midbrain nerve cells whose loss is the hallmark of the condition, from every Parkinson’s patient sampled — familial and apparently sporadic cases among Caucasians. Curiously, treatments are known, but genetic tests reveal that the majority of sporadic Parkinson’s cases are familial, the vast majority are sporadic. 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 in 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, the question of what causes the death of these dopamine-producing midbrain nerve cells in Parkinson’s has occasioned many 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.

MitoPark

Mitochondria produce energy and 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 nerve cells enriched for dopamine-producing midbrain nerve cells, for Parkinson’s 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, midbrain, 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’ disintegrating by an antioxidant, lower Miro concentrations, in those cells, compensated for their Miro-chopping impairment.

In a fruit-fly model of LRRK2 linked-Parkinson’s disease, Wang’s team observed that mutant LRRK2G2019S fly embryos that developed from eggs of flies carrying their mutant Parkinson’s gene and five from familial patients with other mutations.

Six hours after biochemically inducing mitochondrial damage in this group, the scientists broke open some of these cells to observe signs of Miro degradation. At 14 hours post-biochemical assault, they broke more cells open to inspect 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.

They then employed techniques ranging from live imaging with microscopic cameras to biochemical manipulation to show that damaged mitochondria in the dopaminergic nerve cells generated from healthy 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 their death, 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.

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

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 Hematology/Oncology and the Blume Foundation, was awarded $195,000 from the foundation’s R. Hope Hope Fund to study methods to improve stem cell therapy and to study the likelihood of graft-versus-host disease is reduced while maintaining graft-versus-leukemia effect.

Lora Schultz, MD, instructor of pediatrics, was awarded $330,000 to develop targeted methods to disrupt inhibition of anti-tumor immune cells.
Retinoic acid

versely, 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.

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 protein should feel, how they actually felt. Contreras said, "I feel like if I saw the face, my hands would be shakey," said Tim Chai, 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."

"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 Petros, former clinical fellow Michael DiMaio, MD; postdoctoral scholars Naranth Reticker-Flyn, PhD, Justin Kenkel, PhD, Yaron Carmi, PhD, and Hyeswan Leeong-Youn, 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.

"Inhibiting retinoic acid activity significantly increased the tumor burden."
Sleep continued from page 1

is the senior author. The lead author is postdoctoral scholar Ada Ehejiriri Echeta.

“This has potential huge clinical relevance,” de Lecea said. “Insomnia, a multimillion-dollar market for pharmaceutical companies, has traditionally been treated with drugs such as benzodiazepines that non-specifically shut down the entire brain. Now we see the possibility of targeting 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, but there are no one-size-fits-all solutions, 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 is, “How’s your sleep?”

Similarity across vertebrates

The reward-system 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 clusters to many parts of the brain, 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.

For the new study, the investigators employed male laboratory mice bioengineered in several respects to enable the use of advanced technologies to remotely excite and monitor activity of a subset of 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 observed behavior 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, cells emanating from the VTA rose on waking and stayed elevated when mice were awake. Conversely, cells emanating from the VTA rose on waking and stayed elevated when mice were awake. Conversely, cells emanating from the VTA rose on waking and stayed elevated when mice were awake.

“This is the first finding of a sleep-preparation starter circuit in the brain with benzodiazepines, such as Valium, that knock out the entire brain.” He said he also sees the possibility that drugs tar-

ging the VTA’s dopamine-secreting nerve cells could benefit those suffering from neurological conditions such as schizophrenia or bipolar disorder that are characteristic of 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 Klorman Family Foundation and the Edmond and Lily Safra Center of Brain Science.

Stanford’s Department of Psychiatry and Behavioral Sciences also supported the work.

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 women’s treatment choices. Women can learn more at http://med.stanford.edu/studies.

The study’s principal investigators are David Spiegel, MD, professor and chair of psychiatry and behavioral sciences; and the Stanford Center on Stress and Health; Amit Erkin, MD, PhD, associate professor of psychiatry and behavioral sciences; James Gross, PhD, professor of psychology; and Allison Kustrin, 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, 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 questions to see what specific parts are doing six, 12 and 18 months later.”

The researchers plan to recruit 150 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-studies@stanford.edu.
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 well-being, 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.

Let’s 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 Interventional**

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 an opportunity 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.

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

**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.

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.

**OF NOTE**

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 $2 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 a professor and chair of ophthalmology, and Huberman is associate professor of neurobiology. Their research focuses on using large national databases to assess the cost, quality and effectiveness of care.

MICKEY HU, PhD, associate professor of obstetrics and gynecology, received a $2.5 million grant from AvON’s 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 improve 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 Jan. 1. Her research focuses on immune detection of intra-cellular 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.

JENNIFER RAYMOND, PhD, was promoted to professor of neurobiology, effective July 1. She specializes in urologic oncology, and her research focuses on investigating new therapies for renal, prostate and other types of cancer.

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

ANAND VEERAVAGU, MD, was appointed assistant professor of neurosurgery, effective July 1. He is the director of minimally invasive neurosurgery 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.

By Jennie Dusheck