Breast cancer patients who underwent a lumpectomy followed by radiation therapy survived as long as patients who had a bilateral mastectomy, according to a large study conducted by researchers at the School of Medicine and the Cancer Prevention Institute of California.

The comprehensive analysis of nearly 190,000 California women with the disease is the first to directly compare survival rates following the three most common surgical interventions: bilateral mastectomy (the removal of both breasts), unilateral mastectomy (the removal of the affected breast), and lumpectomy (the selective removal of cancerous tissue within the breast) plus radiation. Women in the study were diagnosed between 1998 and 2011 with cancer in one breast.

The study was published Sept. 2 in the Journal of the American Medical Association.

The researchers sought to understand why increasing numbers of women are choosing bilateral mastectomies after a diagnosis of cancer in just one breast. The study found that, in 2011, as many as 12 percent of newly diagnosed breast cancer patients opted for a bilateral mastectomy, despite uncertainty as to whether this approach was better than the alternatives. This study dispels much of that uncertainty.

“We can now say that the average breast cancer patient who has bilateral mastectomy will have no better survival than the average patient who has lumpectomy plus radiation,” said Allison Kurian, MD, an assistant professor of medicine and of health research and policy at Stanford. “Furthermore, a mastectomy is a major procedure that can result in a slightly lower quality of life and a slightly longer recovery period.”

The study did find, however, a very small marginal survival benefit in women who underwent a mastectomy and opted to have their breast reconstruction performed after surgery.

A co-author of the study, Scarlett Gomez, is a doctoral student in chemical and systems biology. She and her team genetically engineered yeast cells to “brew” opioids in a way that eliminates the need to grow poppies, allowing us to reliably manufacture essential medicines while mitigating the potential for diversion to illegal use,” Smolke said.

The research is described in a paper that was published Aug. 24 in Nature Chemical Biology. Smolke is the senior author, and the lead author is Kate Thodey, a doctoral student in chemistry, is the other co-author.

In the paper, the researchers detail how they added five genes from two different organisms to yeast cells. Three of these genes came from the poppy itself, and the others from a bacterium that lives on poppy stalks.

This gene mashup was required to turn yeast into cellular factories that replicate two separate processes: how nature produces opium in poppies, and how pharmacologists use chemical processes to further refine opium derivatives into modern opioid drugs, such as hydrocodone.

Morphine is one of three principal painkillers derived from opium. As a class, they are called opiates. The other two important opiates are codeine and hydrocodone.
How did this whole issue begin to germinate?

RELMAN: It was really the re-ignition of an issue that has percolated for many, many decades in biology. If you were to step back and think about some of the earlier incarnations of this discussion, it would take you back to the 1970s — to the early debate about the possible risks associated with recombinant DNA technology.

In recent years, it’s become a more frequent topic of discussion, I think, because of the ongoing revolution in the biological sciences and the heightened risks and benefits that arise from our newfound capabilities in the laboratory. Scientists today routinely achieve goals that one could only dream about back in the 1970s.

I want to be clear: I am not opposed to laboratory work on dangerous pathogens, especially if they are known to exist in nature. Rather, I am opposed to high-risk experiments and, in particular, those that seek to create novel, dangerous pathogens that cannot be justified by well-founded expectations of near-term, critical benefits for public health — benefits that clearly outweigh the risks, and benefits that cannot be achieved through other means.

Unfortunately, there are increasing examples of errors and mistakes that have occurred through either careless or simply imperfect human behavior. These errors take on much greater consequence when the work involves transmissible agents.

What concerns you most about the creation of these pathogens? What’s the greatest fear you have?

RELMAN: My greatest fear is that someone will create a highly contagious and highly pathogenic infectious agent that does not currently exist in nature, publish its generic blueprint, allow it to escape the laboratory by accident, or else enable a malevolent person or persons to synthesize the agent with the intention of releasing it into the world.

I think it’s very important that we include nonscientists, but we then need to make sure that they understand the science well enough to be able to participate in a discussion that includes technical issues.

The Scientists for Science contend that, in contrast to genes, recombinant DNA technology, to include outsiders in the early discussions about the appropriateness of the experiments and the management of risk. They invited the press. They invited some lawyers. They invited a lot of people who thought they could represent other segments of society, because the work was very important for the future, which I can then try to weigh against the next year or so, not just at some ill-defined time in the future, which is really a slippery slope toward tacit acceptance of any experiment that any scientist might propose as of interest.

We need to fall back on the assumption that all science that a well-meaning, or seemingly well-meaning, scientist undertakes is done for the benefit of the knowledge that might ensue. What I worry about, though, is the increasing number of experiments that are undertaken not because someone has thought about the discrete benefits for society, but because the experiment just seemed cool, neat, or based on an I-wonder if-it-can-be-done kind of approach.

When you’re dealing with disease-causing organisms — especially if you deliberately manipulate them to see if they can become even more virulent or transmissible — you have the obligation to say, “An experiment shouldn’t simply be done because it’s interesting or cool or I wonder if it can be done.”

You have to be extremely mindful of the risks that you’ve accepted for yourself and for everyone else, in doing that experiment. You have to stop and say, “What are the real concrete benefits that we will all realize in the next year or so, not just at some ill-defined time in the future, which we can try to weigh against the risks that this experiment also brings?”

A worker at a Centers for Disease Control and Prevention laboratory harvests avian influenza virus H7N9, which already exists in nature.

A phenomenon known as “sleep drunkenness” may be more common than previously thought.

By Ruthann Richter

A phenomenon known as “sleep drunkenness” may be more common than previously thought, affecting as many as 1 in 7 adults, according to a new study led by a School of Medicine researcher.

That means as many as 36 million Americans experience this potentially problematic sleep condition, in which they are awakened suddenly in a confused state and may be prone to inappropriate behavior, poor decision-making or even violence.

In interviews with nearly 16,000 adults ages 18 to 102, the researchers found that within the previous year, 15.2 percent experienced the condition, also known as confusional arousal, with more than half saying they had at least one episode a week.

Sleep specialist Maurice Ohayon, MD, DSc, PhD, professor of psychiatry and behavioral sciences at Stanford, said he was surprised at the extent of the problem and particularly the length of time that people reported feeling confused and disoriented following a sudden awakening, whether at night or from a daytime nap.

“I was thinking maybe 30 seconds, a minute, 2 minutes,” said Ohayon, who is the lead author of the study. “When you ask people, 60 percent said it lasted more than 5 minutes. And one third said it was 15 minutes or more. A lot of things can happen in that time.”

“The concern is that people in a job of some responsibility could be in the situation because their memory is impaired,” he added. “Their judgment is not taking into account the environment around them, so they can have a bad day.”

By Ruthann Richter

David Relman on risks of creating new pathogens

David Relman, MD, a professor of infectious diseases and of microbiology and immunology, and co-director of the Center for International Security and Cooperation, is a member of the Cambridge Working Group. The coalition of scientists argues that the creation of potential pandemic pathogens in labs should be curtailed until the benefits and risks of such work, as well as how it’s conducted, can be better assessed.

Calculationally, when the group formed earlier this summer, half of the public was just beginning to learn about back-to-back mistakes involving dangerous pathogens — anthrax, H5N1 flu virus and smallpox — in government labs. In a statement, the Cambridge group says the incidents “remind us of the fallibility of even the most secure laboratories, reinforcing the urgent need for a thorough reassessment of biosafety.”

Yet another group, calling itself Scientists for Science, was created in the wake of the Cambridge statement to promote the usefulness of experiments on dangerous pathogens and to argue against limiting them.

But at Relman, a biosecurity expert and the Thomas C. and Joan M. Merigan Professor, points out, the two sides are not too far apart in their views. He recently responded to some questions from Paul Costello, chief communications officer at the School of Medicine, about the debate.

3 heard you say on NPR’s “Morning Edition” that you wanted a larger public debate of this issue. What do you mean by that? How would you like to see the public engaged?

RELMAN: In the 1970s — in 1975, in particular — there was the famous Asilomar Conference, which took place down on the Monterey Peninsula near Pacific Grove. There was a deliberate effort by the scientists at that meeting, who were the pioneers of recombinant DNA technology, to include outsiders in the early discussions about the appropriateness of the experiments and the management of risk.

I think it’s very important that we include nonscientists, but we then need to make sure that they understand the science well enough to be able to participate in a discussion that includes technical issues.

The Scientists for Science contend that, in contrast to genes, recombinant DNA technology, to include outsiders at the Asilomar, studies on dangerous pathogens are already subject to extensive regulations. How do you respond to that?

RELMAN: What they say is true. Furthermore, I think the vast majority of those who have spoken about risks in science actually appreciate the much larger benefits that are usually a part of the science that we all do.

I began my career working on pathogens, on disease-causing bacteria. I fully believe that that kind of work, in general, is absolutely essential. We don’t have any disagreement on that. The place where we may disagree is on whether we are willing to acknowledge that there may be experiments — probably few and far between — that perhaps ought not to be undertaken because of an unusual degree of risk. Just because a scientist can think up an experiment doesn’t mean it should be performed.

5 said you in the NPR interview, “Every time that one of these experiments comes up, it just ups the ante a bit. It creates additional levels of risk that force the question, Do we accept all of this?” Can you expand on that?

RELMAN: Yes. I’m concerned because it almost feels as though over the past, say, five years, we’ve been on what’s really a slippery slope toward tacit acceptance of any experiment that any scientist might propose as of interest.

We need to fall back on the assumption that all science that a well-meaning, or seemingly well-meaning, scientist undertakes is done for the benefit of society, but because the experiment just seemed cool, neat, or based on an I-wonder if-it-can-be-done kind of approach.

When you’re dealing with disease-causing organisms — especially if you deliberately manipulate them to see if they can become even more virulent or transmissible — you have the obligation to say, “An experiment shouldn’t simply be done because it’s interesting or cool or I wonder if it can be done.”

You have to be extremely mindful of the risks that you’ve accepted for yourself and for everyone else, in doing that experiment. You have to stop and say, “What are the real concrete benefits that we will all realize in the next year or so, not just at some ill-defined time in the future, which I can try to weigh against the risks that this experiment also brings?”

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu.

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In recent years, it’s become a more frequent topic of discussion, I think, because of the ongoing revolution in the biological sciences and the heightened risks and benefits that arise from our newfound capabilities in the laboratory. Scientists today routinely achieve goals that one could only dream about back in the 1970s.
Comparing gene expression among flies, humans and worms

By Krista Conger

Fruit flies and roundworms have long been used as model organisms to learn more about human biology and disease. Now, researchers at the School of Medicine have used this approach to learn which proteins and DNA sequences are most important in the body.

The research was conducted as part of a multi-institutional collaborative effort to understand more about how organisms control the expression of their genes to generate normal behavior, muscles, skin, blood and all of the other types of cells and tissues necessary for complex life—all at the exact right time and place in the body.

The fruits of modENCODE

The project, known as modENCODE, is an extension of the ENCODE Project, an international effort that was launched in 2003. As part of the large collaborative project, which was sponsored by the National Human Genome Research Institute, researchers published more than 4 million regulatory elements found within the human genome in 2012, known as binding sites, these regions of DNA serve as landing pads for proteins and other molecules known as regulatory factors that control when and how genes are used to make proteins.

In the most recent example, modENCODE, brings a similar analysis to key model organisms like the fly and the worm. Snyder is the senior author of two of the papers that were published Aug. 28 in two leading journals.

In one previous study, researchers found that for glaucoma patients, the optic nerve fiber. The mechanism—moves back and forth in the fluid and the gas—pushes back and forth in the eye. People during confusional arousal—"a state in which awareness has been reduced to a minimum"—may be confused and disoriented. He said people who experience frequent episodes of confusional arousal are at greater risk for sleepwalking, and that to help them fall asleep may be confused.

For the 2.2 million Americans battling glaucoma, the main course of action for staying off blindness involves weekly visits to eye specialists, who monitor — and control — increasing pressure in the eye.

Now, a tiny eye implant developed at Stanford could enable patients to take more frequent readings from the comfort of their homes. Reducing the need for hourly measurements of eye pressure could help doctors tailor more effective treatment plans.

"For me, the charm of this is the simplicity of the device," said Stephen Quake, PhD, professor of bioengineering, and ophthalmologist Yossi Mandel, MD, PhD, MHA, of Bar-Ilan University in Israel are the senior authors of the paper. The lead author is Ismail Ohayon, MD, postdoctoral scholar in Quake’s lab.

Intraocular pressure is the main risk factor associated with glaucoma, which is characterized by a continuous loss of specific retina cells and degradation of the optic nerve fiber. The mechanism linking IOP and the damage is not clear, but in most patients IOP levels correlate with the rate of damage.

Measuring IOP at normal or below-normal levels — usually with medicaments or surgery — is currently the only treatment available for glaucoma that requires repeated measurements of the patient’s IOP until the levels stabilize. The problem, though, is that the readings do not always tell the truth.

By Bjorn Carey

Sleep

continued from page 2

they will probably have a bad response. The response will not be adapted to the environment.

The study was published Aug. 28 in Nature Medicine. Quake, who is also the Stanford professor and chair of genetics, said he was surprised to discover a strong link between the condition and the use of antidepressants, which likely modify sleep architecture and may contribute to a greater incidence of the condition.

Though there is a common perception that people who take sleep medications to help them fall asleep may be confused, the research indicates that they wake up completely alert, as well as people with certain psychiatric disorders, such as major depression, anxiety and alcohol dependence, the researchers said.

Also surprising, they said he was pleased to discover a strong link between the condition and the use of antidepressants, which likely modify sleep architecture and may contribute to a greater incidence of the condition. Though there is a common perception that people who take sleep medications to help them fall asleep may be confused, the research indicates that they wake up completely alert, as well as people with certain psychiatric disorders, such as major depression, anxiety and alcohol dependence, the researchers said.

They may feel agression toward their partner or the people who have awakened them.

"It's critical to catch things before they go off the rails because once you go off, you can go blind. If patients could monitor themselves frequently, you might see an improvement in treatments."

A paper describing the device was published online Aug. 24 in Nature Medicine, Quake, who is also the Lee Orcowitz professor of bioengineering, and neurologist Michael Snyder, PhD, published online Aug. 28 in the Proceedings of the National Academy of Sciences, describing some aspects of the modENCODE project, which has led to the publication, or upcoming publication, of more than 20 papers in a variety of journals.

Postdoctoral scholar Carlos Araya, PhD, is the lead author of one of the Stanford papers, which mapped the binding sites and cellular expression patterns of 92 regulatory factors in the laboratory roundworm C. elegans; former graduate student Alan Boyle, PhD, shares lead authorship with Araya on the second paper, which compares the newly generated roundworm data with human and fruit fly regulatory factors to identify regions of similarity and difference among the organisms. Research associate Triupri Kawi, PhD, coordinated the research in the Snyder lab and is a co-author of both papers.

The researchers compared this information between the fly and the worm at several stages of development to learn which proteins and DNA regions are most important at each stage. They also identified which individual cells within the worm were generating, and the regulatory factors at each stage.

“For the first time we’re now able to follow in detail where and when particular regions in the genome are active, and which genes are regulated in different cells in which they are operating with an unprecedented level of accuracy,” said Snyder, who is also the Stanford W. Asherman, MD, FACS, Professor in Genetics.

HOT spots

Many of the regulatory networks or “rules” identified by the researchers are shared among the three organisms. For example, most genes in all three organisms are expressed in the same cells or structures, suggesting they target—spots in nearby DNA. These HOT spots contain clusters of regulatory regions important for the control of gene expression. However, the identities of the regulatory elements bound to the sites differedaccording to the stage of development of the organism, the cell type and the three-dimensional structure of the DNA at that location.

The exact protein players and DNA sequences involved in binding to or serving as the HOT spots also often differed among human, fly and worm—perhaps reflecting different evolutionary pressures. These differences are a likely reason why flies, worms and humans are so distinct in shape, size, and behavior for example.

The wealth of data from the modENCODE project will fuel research projects for decades to come, according to Snyder.

“We now have one of the most complete pictures ever generated of the regulatory regions and factors in several genomes,” said Snyder. “This knowledge will be invaluable to researchers in the field.”

Additional Stanford authors are postdoctoral scholars Dan Xie, PhD, and Yong Cheng, PhD; research assistants Lixia Jiang and Beijing Wu; former researcher associate Cathleen Brdlik, PhD; software developer Philip Caring; and assistant professor of genetics and of computer science Anshul Kundaje, PhD.

The study was supported by the National Human Genome Research Institute and Stanford’s Department of Genetics also supported the work.

By Bjorn Carey is a science writer for the Stanford News Service.
By Becky Bach

First Health 4 All fellows cross finish line, showcase projects

Charles Bowden, MD, seemed to have it all. For decades, he’d built a successful career practicing medicine and developing drugs and medical devices. Yet despite his professional accomplishments, Bowden said he felt like he was making only a “marginal” difference.

He took a chance and enrolled in Stanford Health 4 All, a new, nine-month fellows program that incorporated coursework on preventive health and hands-on community internships. (Until August, the program was known as Stanford Health 4 America.)

As part of the program, the fellows complete a service-learning or research-oriented project. For his project, Bowden examined a group of “super-users” of the Stanford Hospital Emergency Department. He discovered that in fiscal year 2013, 123 patients visited the Hospital’s emergency department.

The programs concluded at an Aug. 28 ceremony on campus, but Bowden said he plans to continue working with them on an ongoing, more appropriate care. He said the program gave him the tools, courage and “breathing space” to tackle big problems.

“You go through such a long application process, and now it’s actually all going to start,” said Phansalkar, grinning while taking photos with her family just prior to the ceremony on Alumni Green. “It’s really exciting. It’s a little surreal.”

Phansalkar, a graduate of the University of Connecticut, joined fellow members of the incoming cohort of 90 medical students, selected from an applicant pool of 7,450, for this year’s ceremony. Each student walked across a stage to be garbed in a white coat and accept his or her own stethoscope, the trademark instrument of physicians.

“The next four years will change the way you look at and see the world,” said Lloyd Minor, MD, dean of the medical school, addressing the students and their family members and friends, as well as faculty. “You will learn some of life’s most valuable lessons from your patients.”

The ceremony concluded a week of new student activities, which began with a camping trip Aug. 16-19 to Lake Alpine in the Sierra Nevada Mountains, followed by three days of orientation, which included an informational meeting about the newly created Office of Medical Student Wellness.

“You’ll have to be like a robot to start medical school without some uncertainties,” said Rebecca Smith-Coggins, MD, professor of surgery and associate dean for medical student life advising, who told the students the new office was open to them for all nonacademic issues, including one-on-one confidential advising. The office was created to enable a respectful learning environment and provide counseling to students on personal matters, Smith-Coggins said.

In his address, the dean highlighted some demographics of the new class. Fifty-one percent of you are women; 15 percent of you are from communities under-represented in medicine; 21 of you were born outside of the U.S., coming from China, Columbia, India, Vietnam, just to name a few, he said. “You come from a diverse and wide range of universities — 10 of you from Stanford, 13 from the Stanford of the East (Harvard). Eighteen of you already have a master’s or a doctorate, and many of you have already published research, participated in varsity athletics, studied in the arts and contributed to your community.

The new class also includes 16 MD/PhD students, an unusually large number, reflecting the school’s aim to train more physician-scientists in light of a worrisome decrease in their numbers nationally, said PJ. Utz, MD, professor of medicine and director of the Medical Scientist Training Program.

“I love the idea that you can be a physician and scientist,” said Phansalkar, one of the new MD/PhD students, who said her research interests are in the field of computational biology. “You get to be on the front line to see what the patient needs, and then go back and develop those needs in the lab.”

The bestowing of stethoscopes on students emphasized the importance of a doctor’s connection with a patient, said Laurie Weisberg, MD, president of the Medical Center Alumni Association.

“The stethoscope is one of the prime symbols of patient care and the practice of medicine,” Weisberg told the audience. “The great thing about the stethoscope is you have to be close to your patient to use it. This is your chance to truly interact with the patient. You are listening to what the patient has to tell you.”
Researchers take up challenge of reviving cartilage

By Sara Wykes

Constance Chu was a medical student observing a surgery performed by her teacher when she caught her first glimpse of human articular cartilage, the smooth, glistening coating that covers the ends of bones as they meet at the ankle, knee and hip.

"People were acting like I was crazy," she said, "but that was a chance at this," her teacher, Henry Mankin, MD, chief of orthopaedic surgery at Massachusetts General Hospital, told her. "If you damage this cartilage, it doesn't grow back."

In the early 1990s, and Mankin was considered one of the 20th century's leaders in research on cartilage—especially articular cartilage, which is thought to be especially prone to injury because it lacks nerves and blood, the body's two most important tools for healing. Its basic metabolism was believed to be so slow that any cartilage wound would not heal. With that set of characteristics, the only hope for damaged joints was to replace them with something artificial.

Now a Stanford professor of orthopaedic surgery, Chu takes the kind of cartilage and ligament injuries that typically lead to joint replacement. She is convinced, however, that articular cartilage can heal itself. She and several Stanford colleagues are researching ways to predict and track the damage to this all-important bone protector, to find new treatments and to stem the rapidly rising flood of people whose joints are wearing out.

"The next generation of orthopaedic devices," said William Maloney, MD, professor and chair of orthopaedic surgery at Massachusetts General Hospital, told her, "is going to be biologic in nature: protein and cells, not metal and plastic."

Cartilage research has only recently gained wider interest. In fact, when she was a young researcher looking for ways to grow cartilage from stem cells and to capture images of articular cartilage behavior, Chu said, "people were acting like I was crazy. Now everybody wants to be able to do it."

Main driver of knee and hip replacements

Understanding articular cartilage is at the heart of that next generation of orthopaedic devices, pushed by a rapidly rising need for joint replacement. Many people are living long enough to become them in the United States— are familiar with the pain caused by damaged articular cartilage, otherwise known as osteoarthritis. That condition is expected to increase sharply in the next generation for the knee and hip replacements already given to more than 7 million Americans. Osteoarthritis is distinctly age-related, so the aging of the baby boomers will push even higher the numbers who suffer from osteoarthritis and the joint replacements that usually follow.

"The next generation of orthopaedic devices is going to be biologic in nature: protein and cells, not metal and plastic." Orthopaedists are aiming their work at the key characteristics of the interaction of those two materials and their interface with bone and with the bone of the other joint, the soft tissues that surround the joint and the blood supply that enters and leaves through that.

Confronted with so much, the only hope for damaged cartilage—otherwise known as osteoarthritis. That condition is the primary impetus for the knee and hip replacements that usually follow.

"Mother Nature did a brilliant job of engineering," said Jason Dragoo, MD, associate professor of orthopaedic surgery at Stanford, "to the point that it is difficult to understand how it works."

"It is one of the body's most complex tissues."

If researchers succeed in recreating articular cartilage, it won't be the first time that a natural substance has been chosen to replace a damaged joint. The first experiments in joint replacement began in the late 19th century with a German physician who used ivory to replace a young woman's knee. In the 1930s, and an American orthopaedist created a tempered glass called Pyrex before finding a chrome-cobalt alloy to be more durable.

The surgery has evolved since the first total knee replacement in 1968. Surgeons make a long incision from above the inside of the knee down to 2 inches below. The surgeon cleans and prepares the ends of the humerus and the top of the tibia to accommodate the replacement parts. The tibia is capped with a metal covering that mimics its old, rounded end. Into the top of the shinbone, surgeons insert a stem that will be covered with a circular metal covering. On top of that covering rests a similarly shaped layer of plastic whose upper surface is curved inward to accept the rounded end of the tibia. The back of the knee-cap is fitted with a metal or ceramic button. With those components in place, the tibia is rotated around on the shinbone's tray, with the patella in place to cover the joint.

Cell-based cartilage repair

The great hope is that insight into the biology of cartilage will allow damaged cartilage to revive, making such drastic intervention unnecessary.

Clinical trials are taking place around the world to test implants made from cadaver tissue, and new bone and cartilage formation. Many of these materials, however, are not well suited to the conditions inside a joint, which isn't easy to come by. Treatments that rely on the patient's own cells to make replacement cartilage are also plentiful, though not very successful so far, Maloney said. It will take another decade before cell-based cartilage repair will protect joints well enough for any activity that stresses our knees and hips beyond basic movement, he added.

Later this year, Dragoo plans to start testing a knee joint repair treatment that uses stem cells from the fat pad under the knee capsule as a repair material. He will harvest the stem cells from a small amount of cadaver tissue, put them in a centrifuge to concentrate them, add bio- logic glue made from blood, and insert that mix into the cartilage defect. He will instruct a 3-D printer to re-create articular cartilage. That may be possible in a couple of years on a small scale. "It is a question of scale to test as a repair for the pothole version of cartilage defects," Dragoo said. "We will then be able to generate cartilage."

Even more reliable, however, will be the ability to instruct a 3-D printer to re-create articular cartilage. That may be possible in a couple of years on a small scale to test as a repair for the pothole version of cartilage defects. Dragoo said, "then we can reconfigure the whole structure.

Preventing cartilage damage

Other Stanford researchers are focusing not only on better understanding how to work with transplanted cartilage, but also on how to prevent and predict cartilage damage. Marc Safran, MD, professor of orthopaedic surgery, has years of experience treating athletes' cartilage injuries. He and Gary Gold, MD, a professor of radiology, are studying the knees of marathon runners using imaging to capture what the stress of running does to cartilage, and to investigate ways to prevent such damage. Safran has also been identifying the anatomic differences that make someone more vulnerable to joint damage. "If we can prevent this damage from happening, that will be the real key," he said.

That kind of research is valuable because articular cartilage can be damaged by more than just the aging process. If the contact points of the knee joint are altered, then the cartilage's protective barrier no longer makes contact properly. And the most-often damaged element of that arrangement is the anterior cruciate ligament, or ACL. Young athletes who tear their ACLs set in motion a deterioration of cartilage that can lead to early osteoarthritis and the need for joint replacement.

Cartilage and the discs between vertebrae in the spine have many similarities. Another professor of orthopaedic surgery, Serena Hu, MD, has focused on the discs of the spine, searching for new ways to preserve disc strength and function. "Understanding more about the genetics of disc degeneration will help us determine who will benefit from early intervention," Hu said.

When Chu started her career, she was one of only a few researchers working on articular cartilage, but now she has plenty of collaborators. In fact, the International Cartilage Repair Society, formed in 1997, now has more than 1,300 members in 64 countries. At Stanford, Chu and Tom Andriacchi, PhD, a professor of mechanical engineering and of orthopaedic surgery, are studying how abnormal movement patterns damage articular cartilage. She is working with Gold, the radiologist, on the next generation of MRI techniques to detect cartilage behavior. And she is collaborating with Bill Robinson, MD, PhD, an associate professor of medicine, to develop a blood test "to give us an idea of what is going on with articular cartilage without having to do imaging," she said.

But her longest-running project, funded since 2006 by the National Institutes of Health, seeks a way to diagnose osteoarthritis noninvasively before joint damage begins. The current method for diagnosis, arthroscopy, is a surgical procedure in which a camera is inserted inside the joint.

So Chu is thrilled by the results of one of her recent experiments, published this summer. The study examined the ability of a new imaging technique called ultrashort echo time MRI mapping to assess cartilage health. It was a small study of 42 subjects: 31 with ACL tears, and 11 without. It showed that the MRI method was able to detect damage, and something far more exciting: that articular cartilage could recover. It took time, but after a new type of ACL reconstruction, a year of rest, most of the subjects' injured cartilage did heal.

A version of this article originally appeared in the summer issue of Stanford Medicine magazine.

Several Stanford researchers are working to predict and track damage to articular cartilage, find new ways to treat it and stem the rapidly rising flood of people whose joints are wearing out.
Targeted brain stimulation aids stroke recovery in mice

By Bruce Goldman

When investigators at the School of Medicine ap-
plied light-driven stimulation to nerve cells in the brains of mice that had suffered strokes several days earlier, the mice showed significantly greater recovery in mo-
tor ability than mice that had experienced strokes but whose brains were not stimulated.

This finding was published online Aug. 18 in Proceed-
ings of the National Academy of Sciences, could help iden-
tify important brain circuits involved in stroke recovery and usher in new clinical therapies for stroke, includ-
ing optogenetics, an emerging field of electrical brain-stimulating devices similar to those used for treating Parkinson’s disease, chronic pain and epilepsy. The findings also highlight the potential of using optogenetics to enhance recovery technologies such as tPA, which is administered to increase blood flow to the brain’s primary motor cortex, which is involved in walking.

David Keller and his colleagues deployed optogenetics, a technology pioneered by co-author Karl Deisseroth, MD, PhD, professor of psychiatry and behavioral sciences and of bioengineering. Optogenetics involves expressing a light-sensitive protein in specifi-
cally targeted brain cells. Upon exposure to light of the right wavelength, this light-sensitive protein is activated and causes the cell to fire.

In the study, the Stanford investi-
gators used optogenetics to enhance recovery from stroke in mice — the stimulations promoted recovery even when initiated five days after stroke occurred.

In this study, we found that direct stimulation of a particular set of nerve cells in the brain — nerve cells in the motor cortex — was able to substantially en-
hance recovery after a stroke. By the time they arrived at a medical center, the damage is already done. No pharma-
cological therapy has been shown to enhance recovery from stroke from that point on.

Enhancing recovery

Although the results of this study are encouraging, the researchers say there is still much to be learned about how optogenetics can be used to enhance recovery from stroke.

“Other brain regions after a stroke might be equally or even more effective — this varies greatly among patients depending on the size of the stroke, distance they travelled along the rotating beam before falling off or how fast they walked,” said the study’s lead author, Mi-

Gary Steinberg

The study was funded by the National Institute of Neurological Disorders and Stroke, Russell and Eliza-

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Mastectomy

continued from page 1

survival rate among women who under-
went a unilateral mastectomy.

The results also suggest ways of improving the study. Scarlett Gomez, PhD, a research scientist at CPMC, is the senior author.

The difference in the long-term sur-
vival rates between women who under-
went a bilateral mastectomy and those who received a lumpectomy plus radia-
tion was not statistically significant.

The slightly higher survival rate among women who underwent a uni-
lateral mastectomy could be explained by the fact that these pa-
tients tended to be members of racial or ethnic minorities or have a lower so-
cioeconomic status than other groups, or both, the researchers said.

In 2011, as many as 12 percent of newly diagnosed breast cancer patients opted for a bilateral mastectomy. In contrast, women who received a bilateral mastectomy were more likely to be middle- or upper-
class, younger than 50 or non-Hispanic white or some combination of these factors.

The researchers found that of the 189,734 women in the study, 55 percent received a unilateral mastectomy and 45 percent underwent a lumpectomy, radiation, chemotherapy, or some combination of these.

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Women’s decisions to undergo mastectomy were influenced by many factors, including their fear of recurrence, their perceptions of their body image, and the social and emotional support they received.

In addition, substances called growth factors, produced naturally in the brain, were more abundant in key regions on both sides of the brain in optogenetically stimulated, stroke-
affected mice than in their unstimulated counterparts. Likewise, certain brain regions of these optogenetically stimulated, post-stroke mice showed increased levels of proteins associated with heightened ability of nerve cells to alter their structural features in response to experience — for example, practice and learning. (Op-
togenetics involves expressing a light-sensitive protein in specifically targeted brain cells. Upon exposure to light of the right wavelength, this light-sensitive protein is activated and causes the cell to fire.)

The registry allows us to do a pop-
ulation-based study to gain a real-world picture of cancer cases in California,” said Kurian. “We can ask and answer questions that couldn’t be answered in a randomized clinical trial.” For example, Kurian and Gomez pointed out that it would not be ethical to assign a woman randomly to one of the three common breast surgical options. But using the regis-

ty, they can simply track who received which intervention.

Despite the fact that women who re-
moved both breasts did not have better outcomes, the researchers noted that rapidly increasing numbers of women are opting for the complex surgery, which requires a long recovery period and pos-

tibly reconstructive surgery.

The bilateral mastectomy procedure is particularly prevalent among non-
white women younger than 40 who have private insurance and receive care at a National Cancer Institute-des-
ignated cancer center. In fact, 33 percent of women under age 40 received bilateral mastectomies in 2011, compared with 24 percent in 1998. The trend among bilateral mastectomy in all patients in the study increased from 2 to 12.3 percent during the same time period.

In contrast, racial or ethnic minori-
ties and women with public insurance, such as Medicaid, were more likely to receive a unilateral mastectomy.

The authors emphasize that the study’s findings don’t mean that a BRCA1, BRCA2 or other gene mutation known to significantly increase the risk of developing breast cancer, or with a strong family history of breast cancer, should not get a bilateral mastectomy.

There are also other reasons why a woman might choose a bilateral mastec-
tomy. Some newer reconstruction methods achieve better symmetry when both breasts are reconstructed simultane-
ously. Removal of both breasts may also alleviate a woman’s fear and worry that a second cancer will occur in her remaining breast, the researchers said.

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cell carcinoma is the second most common cancer in humans. More than 1 million new cases are diagnosed globally each year. The researchers found that a single gene product of the KRAS tumor suppressor gene, KRT2A, occurs more than 80 percent of patients with squamous cell carcinoma. The mutation in KRAS is a gain-of-function mutation that results in an overactive version of the gene product. This mutation is typically found in cells that have undergone abnormal growth control, such as those found in tumors.

The researchers conducted a series of experiments to investigate the role of this mutated KRAS gene in the development of squamous cell carcinoma. They found that the mutated KRAS gene was able to drive the growth of tumor cells in a mouse model. This finding supports the idea that the mutated KRAS gene plays a significant role in the development of squamous cell carcinoma.

The research was supported by a National Institute of Health grant to Dr. Smulevich and colleagues. The study was also supported by the National Cancer Institute and the National Institutes of Health. Dr. Smulevich is a member of the faculty of the Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine.
Nurse in heart program brings personal experience to the job

By Anisse Gross

“Once you cut through the heart it’s never the same. It always needs to be cared for.”

That statement from Christy Sillman, RN, 34, is born of experience. A very personal experience. That’s because Sillman was born with congenital heart disease at a time when these patients weren’t expected to live to adulthood.

Now, as one of the many adult survivors needing lifelong, specialized treatment for her heart, Sillman brings special insights to her work as the nurse coordinator for the Adult Congenital Heart Program at Stanford Medicine.

“My patients tell me that they love talking to Christy because not only is she an exceptional nurse, but she gets it,” said George Lui, MD, medical director of the program and clinical assistant professor of cardiology and pediatrics at the School of Medicine. “They’re excited to speak with someone who has been through it firsthand. Not many programs have this kind of asset.”

The Adult Congenital Heart Program at Stanford, a collaboration between Lucile Packard Children’s Hospital Stanford and Stanford Health Care, brings together the expertise of pediatric and adult cardiology. “Ninety percent of children born with congenital heart disease are surviving into adulthood,” Lui said. “Advances in medical and surgical care have created a large population of adult survivors.”

That population now numbers over 1 million people in the United States, according to the Adult Congenital Heart Association.

Sillman’s story began when she was born in 1980 with tetralogy of Fallot with pulmonary atresia. It’s a heart shape that had I gotten the right care earlier. This motivated me to get more involved.”

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But it does. Susan Fernandes, the program’s director, said it’s estimated that more than 50 percent of adults with congenital heart disease are not receiving specialized care, and are often lost to follow-up care beginning in early adulthood.

“It’s important to know that we don’t cure congenital heart disease,” said Lui. “Instead, we provide lifelong care that patients like Christy need.”

Sillman certainly appreciates that care, and the ability to pay it forward through her work and experience.

“I really like bringing a patient’s perspective to what I do,” Sillman said. “There’s nothing better than getting up in the morning and knowing that your job perfectly fits your passions.”

Anisse Gross is a freelance writer.