Microwaves help to treat patient’s tumors

By Sara Wykes

When Gwen McCane says she’s been to hell and back, it’s hard to believe. Her vibrant personality shines brightly when she enters a room, and she’s happy to share a long list of daily activities. But three years ago, the pain she thought was probably acid reflux was diagnosed as pancreatic cancer. She had chemotherapy and radiation, which beat back the disease. Then it showed up in her liver. At first, she couldn’t find a physician who would treat her. “It’s inoperable, it’s incurable, nothing anybody can do,” she was told. She kept inquiring.

“My brother said, ‘I want you to go to Stanford,’” McCane said. “If anyone tells you that something is inoperable and incurable, let Stanford have the last word on that.”

At Stanford, she found Gloria Hwang, MD, clinical assistant professor of radiology. “She came in and said, ‘No problem. I know what it is,’ and she told me about microwave ablation.” Hwang is an interventional radiologist, a specialist in a field that’s not as well-known or understood as it might be, considering its usefulness in cases like McCane’s. “We use X-rays, ultrasound, CT and occasionally MRI to look into patients so we can get devices into them to kill cancers,” Hwang said. “The great thing is that we don’t need to

Researchers discover toggle switch that determines nature of fat cells

By Louis Bergeron

A toggle switch for controlling whether fat cells lounge inactively in our bodies, like tiny couch potatoes, or get off their cellular sofas and burn up their energy has been discovered by researchers at the School of Medicine.

The finding could open the door to developing new therapies for controlling obesity and the myriad diseases that determine nature of fat cells

By Krista Conger

Mitochondrial Eve and Y-chromosomal Adam — two individuals who passed down a portion of their genomes to the vast expanse of humanity — are known as our most recent common ancestors, or MRCA. But many aspects of their existence, including when they lived, are shrouded in mystery.

Now, a study led by the School of Medicine indicates the two roughly overlapped during evolutionary time: The man lived between 120,000 and 156,000 years ago, and the woman lived between 99,000 and 148,000 years ago.

“Previous research has indicated that the male MRCA lived much more recently than the female MRCA,” said Carlos Bustamante, PhD, a professor of genetics at Stanford. “But now our research shows that there’s no discrepancy.” Previous estimates for the male MRCA ranged from 50,000 to 115,000 years ago.

Bustamante is senior author of the new study, which was published Aug. 2 in Science. Graduate student David Poznik is the lead author.

Despite the Adam and Eve monikers, which evoke time period, study finds Common genetic ancestors lived during roughly same time period, study finds
**Protein bath helps stimulate old marrow to form bone**

By Krista Conger

Bone fractures in the elderly are notoriously slow and difficult to heal. Now, researchers at the School of Medicine have identified a simple way to increase the effectiveness of a surgical process called bone grafting that may significantly speed the growth of new, healthy bone in response to trauma.

In studies involving mice and rabbits, the researchers found that a quick dip in a protein bath helps stimulate old marrow to form bone.

The study's results may contribute to the development of a brain-based test from the School of Medicine has found. Along many neural networks, a new study suggests that the hyperconnected salience network, which is difficult to purify and dissolve in liquids. In 2010, Helms and Roeland Nusse, PhD, a Stanford professor of developmental biology, showed that they could attach the Wnt3a protein to tiny, water-friendly molecular bubbles called liposomes that could be injected directly into lab animals with fractures. The previous study found that this treatment promoted the rapid growth of new bone, but safety concerns about its use in humans remained.

"We've shown that when we temporarily treat bone marrow from aged animals with Wnt3a before transplanting the cells into a fracture site, we see really robust bone formation," said professor of surgery Jill Helms, DDS, PhD. "We've shown that when we temporarily treat bone marrow from aged animals with Wnt3a carboxylate before transplanting the cells into a fracture site, we see really robust bone formation."

Helms is the senior author of the study, which was published in the *Journal of Bone and Joint Surgery.*

Philipp Leucht, MD, a resident in orthopaedic surgery at Stanford, is the lead author.

"Hip fractures in elderly people nearly triple the risk of dying within a year of the injury, and a rapidly aging population demands more effective treatments for this type of trauma," said Helms.

"More than half of bone loss occurs after the age of 40, and we understand very little about how bone regenerates as we age," said Leucht. "Our findings could be easily employed by orthopaedic surgeons in the normal course of bone grafting," said professor of surgery Jill Helms, DDS, PhD. "We've shown that when we temporarily treat bone marrow from aged animals with Wnt3a carboxylate before transplanting the cells into a fracture site, we see really robust bone formation."

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Inside Stanford Medicine  August 5, 2013

Genetic testing improved learning in personalized medicine class

By Tracie White

Students who had their genome tested as part of a groundbreaking medical school course on personalized medicine improved their knowledge of the class materials by an average of 31 percent compared with those who didn’t undergo the testing, according to a study by researchers at the School of Medicine. While the sample size was small — 23 students were part of a small, commercial genetics testing company; eight did not — the results may encourage educators to consider this approach in the future, the authors said.

“These results indicate that learning principles of human genetics is more powerful, and learning is more sustained, when exploring your own data,” said Keyan Sarati, MD, PhD, a former Stanford student who initiated the course, called “Genomics and Personalized Medicine.” Sarati, who is the leader of the current study, is now a urology resident at the Massachusetts General Hospital.

The study was published July 23 in PLOS ONE.

The eight-week elective course was the first in the country to give students in advanced-degree programs the option of personal genotyping as part of the curriculum. It was designed to teach them how the exploitation of knowledge about genetics in the past 10 years could affect the treatment of patients. Since the course was first offered in 2010, the use of genetic testing in clinical care has grown.

The course, which is still being taught, was designed as a way to train future doctors and scientists in the skills necessary to use this new tool. The study, which was based on a pre- and post-course test that was voluntarily taken by the majority of the students in the class, also showed that personal testing and the use of personal genotyping data in the classroom did not appear to cause significant anxiety.

“This was a novel teaching approach,” said Kelly Ormond, co-author of the study and associate professor of genetics. “There is always a lot of interest in whether personalized learning can improve education. … What our study shows is that it might have benefits for some self-selected students, and is worthy of cautious consideration.”

Initially controversial, the course was only approved after a campus task force met regularly for a year to debate the pros and cons of students undergoing genetic testing as part of a class. A number of concerns were raised, including the possibility of learning they could be more susceptible to certain diseases, such as diabetes or Parkinson’s. A number of safeguards were subsequently included as part of the course plan, including complete anonymity as to which students chose to undergo testing.

Sarati conceived of the idea for the course in 2009 as a PhD student in genetics. He was working as a teaching assistant in the first-year human genetics course for medical students. At the time, the course curriculum covered primarily of traditional genetics and didn’t reflect the genomics revolution of the past 10 years. Sarati had also recently undergone his own genetic testing, and saw the educational benefits.

“I was curious about what stories were hidden in my genome, what health risks, what responses to drugs that might be predicted,” Sarati said. “For instance, I learned I might have a higher risk for age-related macular degeneration. That led me to read and learn a lot more about the genetics of that disease than I probably would have otherwise.”

He added: “I wanted to find a way to translate my passion for genomics to all these medical students.”

Study results also showed that 83 percent of students who chose to undergo testing were pleased with their decision. Seventy percent of those who underwent the testing reported a better understanding of human genetics on the basis of having undergone genetic testing. The post-course survey also asked students who underwent the testing whether they made any behavioral changes based on the results; some made lifestyle changes or made appointments with doctors. Some initial behavioral changes were reported. Yet in a previous study involving face-to-face interviews with the same students, no behavioral changes were reported six months after the end of the course.

Other Stanford authors included Konrad Karczewski, a bioinformatician student; and Louanne Hudgens, MD, professor of pediatrics and of medical genetics.

Insider

Study: No signs of ‘embryonic-like’ cells in marrow of adult mice

By Krista Conger

Research on human embryonic stem cells has been a political and religious lightning rod for more than a decade.

The cells long have been believed to be the only naturally occurring pluripotent cells. (Under the right conditions, pluripotent cells can become any other cell type in the body.) But some people object to the fact that the embryo is destroyed during their isolation. Induced pluripotent stem cells, created by experimentally manipulating an adult cell such as a skin or nerve cell, are much more ethically palatable. But many researchers believe these cells, but were in fact the very small embryonic-like (VSEL) cells, but were in fact the very small embryonic-like (VSEL) cells, precursors of key cell-surface genes, Weissman’s study was the first to evaluate the biological potency of the cells.

The research was published online July 24 in Stem Cell Reports. Weissman, who is also the Virginia & D. K. Ludwig Professor for Cancer Research and a member of the Stanford University Institute for Stem Cell Biology and Regenerative Medicine and the Ludwig Cancer Institute, shared senior authorship of the study with Instructor Jun Seita, MD, PhD. Postdoctoral scholars Masanori Miyashita, PhD, and Yasuo Mori, MD, PhD, are the lead authors.

Using a variety of methods, the researchers found that most of the very small cells (<5 micrometers in diameter) particles in mouse bone marrow were not cells, but were in fact cell debris or dead cells with a less-than-normal complement of DNA.

Because it is difficult to use a method to determine actual cell size, they opted to include even larger cells in their subsequent analysis. The researchers defined these cells as described in prior experiments. The study was peer-reviewed and published, the difficulty experienced by other labs attempting to replicate the findings has led the Weissman group to conclude in the paper that “the existence of adult mouse VSELs in the bone marrow remains dubious.”

Other Stanford researchers involved in the work were graduate student James Chen; Seth Karten, MD, an academic research and program officer; and postdoctoral scholar Charles Chan, PhD.

The study was supported by fellowships from the Toyobo Biotechnology Foundation, the Uehara Medical Foundation and the Stem Cell Program, the Japan Society for the Promotion of Science, the National Institutes of Health, the California Institute for Regenerative Medicine and the Leukemia & Lymphoma Society.

Hironumi Nakauchi is a shareholder and a member of the scientific advisory board of having undergone Megakaryon Inc., and a member of the scientific advisory board of Shinonoi Inc. Weissman is a member of the scientific advisory board and is a director of Stem Cells Inc. [..]
‘Dead’ gene comes to life, puts chill on inflammation

By Bruce Goldman

A gene long presumed dead comes to life under the full moon of inflammation, School of Medicine scientists have found.

The discovery, described in a study published July 23 in Life, may help explain how anti-inflammatory steroid drugs work. It also could someday lead to entirely new classes of anti-inflammatory treatments without some of steroids’ damaging side effects.

Chronic inflammation plays a role in cancer and in autoimmune, cardiovascular and neurodegenerative diseases, among others. Anti-inflammatory steroid drugs are widely prescribed for treating the inflammatory states that underlie or exacerbate these conditions.

“Inflammation tells your body something is wrong,” said the study’s senior author, Howard Chang, MD, PhD, professor of dermatology and the recipient of an early career scientist award from the Howard Hughes Medical Institute. “But after it does its job of alerting immune cells to a viral or bacterial infection or spurring them to remove debris from a wound site, it has to get turned off before it causes harm to healthy tissue.”

That appears to be what the ‘undead’ gene does. Chang’s team, which identified it, has named it Lethe, after the stream in Greek mythology that makes the deceased who cross it forget their pasts.

The master regulator of inflammation inside cells — a bulky complex of several proteins, collectively known as NF-kappa-B — is a transcription factor: It can switch genes on and off.

NF-kappa-B also plays a key role in aging. In a study published 2007 in the journal Cell, Chang and his colleagues showed that old skin cells in which NF-kappa-B had mutated and decayed to the point where, it is believed, the process is driven by a dy
ing component, the master regulator’s massive signaling complex falls apart.

“Pseudogenes have been considered to be completely ‘dead’ gene comes to life, puts chill on inflammation

By Bruce Goldman

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Of those IncRNAs, a total of 54 were copied from so-called pseudogenes: DNA sequences that, while they resemble closely genes, don’t code for proteins. More than 11,000 pseudogenes — one for every two protein-coding genes — have been identified in the human genome. Scientists believe pseudogenes are copies of actual genes that, during the replication of some ancestral organism’s germ cell, were accidentally inserted into the genome and, redundant but harmless, came along for the evolutionary ride. Over the intervening eons, these genetic doppelgangers have roamed along the genome, mutated and decayed to the point where, it is believed, they no longer do anything at all.

“Pseudogenes have been considered to be completely silent,” said Chang. “But we got a real surprise. When a cell is subjected to an inflammatory stress signal, it’s like Night of the Living Dead.”

Equally surprising, Chang said, is that different signaling chemicals or microbial components (such as bits of bacterial cell walls or of viral DNA) wake up different groups of IncRNAs. This ‘epigenetic combinatorial code’, as Chang put it, offers a ‘smarter’ way to combat inflammation.

“Other pseudogenes undergo similarly selective awakenings to generate IncRNAs in response to different external inflammatory stimuli,” Chang said. “From the pattern of activated IncRNAs, you can tell what the cell was encoun
ered — a virus, a bacteria or something else.”

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Because some pseudogenes sit near protein-coding genes, they could provide a simple illustration of RNA transcripts from the pseudogenes is simply an artifact of normal transcription of full-fledged protein-coding genes. “There’s a tendency to assume it’s some protein-coding gene that NF-kappa-B is really target
ng, and to downplay the activation of a IncRNA as a noise, a ‘ripple effect’ like the one you see when a boat goes by,” Chang said.

But TNF-alpha failed to activate two nearby protein-coding genes on either side of Lethe. Reciprocally, stimuli that turned these two other genes on didn’t af
tect Lethe. Meanwhile, two other pseudogenes that very closely resemble Lethe were not activated by TNF-al
pha, as Lethe was.

Another surprising finding was that dexamethasone, a commonly prescribed anti-inflammatory steroid drug, activates Lethe. Various other steroid hormones that are not anti-inflammatory and do not activate NF-kappa-B, such as estrogen or D or a male steroid hormone, failed to boost Lethe levels.

“We’re wondering whether there might be ways to artificially raise Lethe levels without steroids. These drugs have potentially deleterious side effects such as elevated blood pressure and blood sugar, thinning of bones and general suppression of the immune system,” Chang said.

The study results suggest that not only Lethe but other pseudogenes undergo similarly selective awakenings to generate IncRNAs in response to different external inflammatory stimuli. “From the pattern of activated IncRNAs, you can tell what the cell was encoun
ered — a virus, a bacteria or something else,” Chang said. “These patterns of activation may be able to serve as an indicator of what kind of inflammatory situation or pathogenic invasion is responsible.”

A third surprise: While NF-kappa-B levels and activ
ity within cells increase with an organism’s advancing age, Lethe is dramatically downgraded with increasing age — but eightfold more so in females. Lethe levels in spleens of older mice, compared with those of young mice, dropped 20-fold in males but 160-fold in females. “This gender-specific difference is not seen in young mice,” Chang said. “Could this have any implications for the increasing occurrence of autoimmunity with advancing age, for autoimmune diseases in humans?”

The study was funded by the Ellison Medical Research Foundation, the Glenn Foundation and the National Institutes of Health. The lead author was postdoctoral scholar Nicole Rapicavoli, PhD. Other Stanford co-authors were senior bioinformatician Kun Qu, PhD; bioinformatician Jiajing Zhang, PhD; and undergraduate student Megan Mikhail.

Stanford’s Department of Dermatology also supported this work.

ANSWER: What you saw on the front page is a super-resolution microscopy image of an oligodendrocyte, the type of brain cell that forms protective insulation around nerve cells.

The branching tendrils wrap around a nerve fiber like an octopus tentacle, spiraling many times to form a thick insulating sheath. How the tendril wraps around axons is still a mystery, but some researchers believe that the process is driven by a dynamic cellular scaffold of actin proteins, signaling molecules (colored green) that are constructed inside the cell by regulatory proteins (colored red). The resulting myelin sheath protects nerve cells from electrical signal interference and leakage. Through a process called ‘remyelination’, speed by about 100 times compared to nonmyelinated nerve cells because the myelin sheath’s hollow interior enables the nerve’s axonal core to conduct electrical signals far faster.

The ‘oligodendrocyte is one of the most beautiful examples of cell specialization in nature,” said Brad Zichero, PhD, the Stanford post-
classic pain signaling researcher who prepared the cultured rat brain cells for imaging. “Being able to visually a 10-foot-square office and costs about $700,000. It consists of precision mo
torized platforms to position the sample; laser microscopes that produce finely patterned illuminations of the sample; scientific cameras; and high-speed computers.”

For more about Stanford’s Neuro

By Kiri Newby, communications manager, the Stanford Center for Clinical and Translational Education and Research.
Potential neurological treatments often advance on shaky evidence

By Krista Conger

Clinical trials of drug treatments for neurological diseases such as Alzheimer’s and Parkinson’s often begin on animal studies that preceded them poorly designed or biased in their interpretation, according to a new study from an international team of researchers. More stringent requirements are needed to assess the significance of animal studies before testing the treatments in human patients, the researchers say.

John Ioannidis is senior author of the new study.

The team — led by John Ioannidis, MD, DSc, a professor of medicine at the School of Medicine and an expert in clinical trial design — assessed the results of more than 4,000 animal studies in 160 meta-analyses of potential treatments for neurological disorders, from Alzheimer’s disease, Parkinson’s disease, stroke, spinal-cord injury and a form of multiple sclerosis. (A meta-analysis is a study that compiles and assesses information from multiple studies of a treatment, or, in a particular condition.) They determined that only eight of the 160 potential treatments yielded the statistically significant, unbiased data necessary to support advancing them to clinical trials. In contrast, 108 of the treatments were deemed at least somewhat effective at the time they were published.

Ioannidis and his collaborators at the University of Ioannina School of Medicine in Greece say that animal studies of potential interventions can be made more efficient and reliable by increasing average sample size, being aware of statistical bias, publishing negative results and making all the results of all experiments on the effectiveness of a particular treatment, regardless of their outcome — freely accessible to scientists.

“Some researchers have postulated that animals might not be good models for human diseases,” said Ioannidis. “I don’t agree. I think animal studies can be useful and perfectly fine. The problem is more likely to be related to the selectivity of availability of information about the studies conducted on animals.” Although the researchers focused here on neurological disorders, they believe it is likely that similar bias exists in animal studies of other types of disorders.

Ioannidis, who directs the Stanford Prevention Research Center, is the senior author of the research, which was published online in PLoS Biology on July 16. Lecture Konstantinos Tzilikis, PhD, and postgraduate fellow Orestis Panagiotou, MD, of the University of Ioannina share authorship of the study. Panagiotou is currently a researcher at the National Cancer Center of the National Cancer Institute’s Division of Cancer Epidemiology and Genetics.

Ioannidis is known for his efforts to strengthen the way that research is planned, carried out and reported. He was called “one of the world’s foremost experts on the reliability of medical research” in a profile published in The Atlantic magazine in 2010. He outlined some of the problems he observed in a 2005 essay in The American Medical Association Journal. “Why most published research findings are false.” The essay is one of the most-downloaded articles in the history of the journal media relations office.

For the new study, Ioannidis and his colleagues evaluated results in a database of the thousands of animal studies compiled over the years through the CAMARADES initiative (Collaborative Approach to Meta-Analysis and Review of Animal Data in Experimental Studies), led by professor Malcolm MacLeod, PhD, from the University of Edinburgh, who is also a co-author of the study.

The team compared the number of experiments in the meta-analyses that would have been expected to yield positive results (based on their predicted statistical power) with the actual number of experiments with published positive results. The difference was striking: 919 expected versus the 1,719 that were published, implying that either negative results were not published, or that the results of the experiments were interpreted too optimistically.

“We saw that it was very common for these interventions to have published evidence that they would work,” said Ioannidis. “It was extremely common to have results that suggest they would be effective in humans.”

Furthermore, nearly half (46 percent) of the 160 meta-analyses showed evidence of small-study effects — a term used to describe the fact that a small study using fewer numbers of animals is more likely to find the intervention more effective than a larger study with many animals.

Ioannidis speculated that a reluctance to publish negative findings (that is, those that conclude that a particular intervention did not work any better than the control treatment) and a perhaps unconscious desire on the part of researchers to find a promising treatment has colored the field of neurological research. Obscuring access to studies that conclude a particular treatment is ineffective, while also publishing positive results that are likely to be statistically flawed, tilts the perception toward the potential effectiveness of an intervention and encourages unwarranted human clinical trials.

“There are no standard rules that guide a decision to move from animal studies into human clinical trials,” said Ioannidis, who also holds C.F. Rehnberg Professorship at Stanford. “Sometimes interventions are tested in humans with very little evidence that they may be effective. Of the 160 analyses we studied, only eight had what we would call strong evidence of potential effectiveness with no hint of bias in the preliminary animal studies. And of these eight, only two have given positive results in humans.”

Ioannidis believes the development of consortiums of groups of researchers studying a particular intervention, coupled with the free sharing of all data about its effectiveness, or lack thereof, is a good first step in reducing bias in animal studies.

Under the current conditions, only a tiny proportion of interventions that have published some promising results in animals have shown to be at all effective in humans. For example, while dozens of treatments on ischemic or hemorrhagic stroke seem to work in the animal literature, almost none of them has worked in humans,” said Ioannidis. “It is hard to believe we could not improve upon that translation record. If we raise the bar for moving into human trials, centralize researchers’ efforts and make all results available, it will be much easier for researchers to know whether they have a potential winner, and it would increase the efficiency of human clinical trials enormously.”

The study was supported by the MRC Trials Methodology Hub at the University of Edinburgh.

Sometimes interventions are tested in humans with very little evidence that they may be effective.”

Microwave continued from page 1

make large incisions in our patients. We can go in with just the poke of a needle.”

McCane’s new tumors were small, but deep inside her liver, the body’s largest organ, which is so rich with blood vessels that any surgery is tricky. When Hwang does microwave ablation, she makes a small incision and, guided by imaging, finds the tumors and applies microwave heat to them to destroy them. The body then absorbs the dead tissue. Many patients go home the same day.

The microwave technology is not new, Hwang said, but its use to treat tumors is recent. It doesn’t require a lengthy hospital stay, it quickly treats tumors that are otherwise difficult to eradicate, and it does so with minimal damage to healthy tissues. Microwave ablation was pioneered for the approach, Hwang said.

“They weren’t too large, and they were in a location that was easy and safe to target.”

McCane also wanted the treatment to be minimally invasive and pain-free. “My mission as a doctor is to offer interventions,” Hwang said. “Before this technology, most people would say if a patient is healthy enough for surgery, then that’s the way to go because then you know you’ve taken the tumor out of the body,” Hwang said. “It’s hard to argue with that.” But many patients, like McCane, can’t tolerate surgery or have tumors that can’t be reached by surgery, Hwang said. “Microwave ablation offers an option for a significant number of people who may feel like they’re out of options. That’s a lot of what we do in interventional radiology — treating the sickest patients who can’t tolerate toxic medications or major surgery.”

We offer them a chance of beating their cancer.”

Now 73, McCane is back to playing golf, continuing her self-esteem workshops at a country juvenile hall, meeting friends to play cards, working in her garden and spending time with her husband of 50 years. When she has a question about her cancer treatment, she can call Hwang and get an animal response. “When you find a doctor that tells you, ‘It’s no problem,’ that helps you not give up. It makes all the difference in the world. I look good today because of my doctors at Stanford.”

“Every day we see people who have a real need, and they’re scared and they want to know they have options,” Hwang said. “My mission as a doctor is to offer them these options — and to offer them newer, better ways of treating their cancers.”

Gloria Hwang
Communication office earns awards for writing, publications

By Susan Ipakitchian

The writing and publications produced by the medical school’s Office of Communication & Public Affairs earned five honors, including two gold awards, from the Council for the Advancement and Support of Education, known as CASE.

For the second consecutive year, the office received the top honor for staff writing in Stanford Medicine magazine. “Stanford Medicine’s entry was far above the strongest of any we reviewed,” the CASE judges wrote. “There was a compelling and interesting mix of stories that were well-researched and creatively written.”

Four other stories included in the staff-writing entry were “The neuroscience of need,” by Charles Goldman; “Brain power,” by Jonathon Rabinovitz; and “Against the odds,” by Krist Newby. Also earning a gold award was a staff-written graphic by Brian Smale that accompanied the “Transition point” story. The judges said the graphic “is deliberately structured to be graphically persuasive, yet the expression is full of a spontaneous joy that speaks to the gift of freedom the medical process granted.”

The news releases produced by the office earned a silver award in the category of special-issue publications. “The magazine explored questions of improved research and medical efficacy, as well as the dangers of breaching patient privacy,” the judges wrote. “The reporting is intellectually engaging and sophisticated. The resulting issue is full of spontaneous joy that speaks to the gift of freedom the medical process granted.”

For the second year in a row, the office won a CASE award in the category of special-issue publications. “The magazine explored questions of improved research and medical efficacy, as well as the dangers of breaching patient privacy,” the judges wrote. “The resulting issue is full of spontaneous joy that speaks to the gift of freedom the medical process granted.”

Feldman said it is uncertain whether VDR affects cells early in the process of becoming a fat cell, causing a final determination of brown or white to be made before the cell actually develops into a fat cell, or whether it is possible for white cells to later develop characteristics of brown fat cells if VDR becomes blocked.

Feldman and Malloy have already begun working on developing a therapy that would use some sort of small molecule to block VDR from inhibiting the production of the UCPI protein. The goal is to keep the VDR from blocking development of brown fat, but not interfere with the receptor’s ability to bind with vitamin D and engage in other processes it regulates, such as calcium homeostasis, Feldman said. “That’s what the utopian therapy would be.”

Study of online-video support group seeks breast-cancer patients from rural areas

By Holly MacCormick

The Sierra-Stanford Partnership is seeking women who have been diagnosed with breast cancer to participate in a study of the effectiveness of support groups conducted via online video.

The randomized clinical trial is designed to help researchers determine whether this type of video-mediated support group improves the well-being and quality of life of breast-cancer patients who live in rural areas. The study also aims to determine whether participants consider the approach feasible and satisfactory.

Half of the patients in the study will participate in a virtual support group; the other half, the control group, will not participate in any kind of support group. All will receive a workbook and will complete questionnaires via a secure Internet link. Volunteers for the study must be 21 or older; have been diagnosed with breast cancer within the past five years; and live in one of 27 specified rural California counties, excluding the following cities: Chico, Madera, Redding, Rocklin, Roseville, and Yuba City. For more exclusion and inclusion criteria, visit http://oneineightysupport.org.

The Sierra-Stanford Partnership is a collaboration between Joanne Hild and Mary Anne Kreshka of the Sierra Streams Institute — both women are rural-community advocates for breast-cancer patients — and Cheryl Koopman, PhD, professor of psychiatry and behavioral sciences at the School of Medicine.

“The women in rural areas have a hard time finding other breast-cancer survivors,” said Cheryl Koopman, PhD, a professor of psychiatry and behavioral sciences at Stanford who is principal investigator in the study. Many wish to communicate with another, but they can face a number of challenges — such as snowed-in mountain passes, limited public transportation and high travel costs — simply getting to support groups, which are frequently located in major cities. Moreover, patients are often too fatigued from cancer treatments to make the trip.

Text-based, Internet support groups are already available, but many patients want a more interactive form of communication. “A lot of women tell us they would like to see the support-group leader and another one,” Koopman said. Koopman said that the strength of the video-based support group is that breast-cancer patients can see and interact with one another with minimal cost and effort, she said.

Volunteers interested in participating in the study should contact Lisa Frankel at (530) 265-2442 or send an email to info@oneineightysupport.org.

The Stanford Cancer Institute and Dr. Susan Love Research Foundation/Avon Army of Women are providing recruitment assistance for the study, which is funded by the California Breast Cancer Research Grants Program.

Fat continued from page 1

than white ones, compared to what was observed in a control group of fibroblasts from healthy volunteers. Earlier studies in mice showed that when VDR is deleted from the genome, those animals have an increased amount of brown fat. But it has been unclear from the earlier work if inhibition of the receptor’s ability to bind with vitamin D and engage in other processes it regulates, such as calcium homeostasis, is important.

This new study shows that the change in the type of fat produced can be regulated independently from the systemic environment. This is also the first time anyone has shown that the effect holds true in human cells.

VDR is known to work by binding to certain small sections of DNA, thereby regulating the expression of particular genes. Uncoupling protein 1, or UCP1, is the protein that is crucial for the production of brown fat. So using fibroblasts, Feldman and Malloy surveyed the human UCPI gene, searching for sites on the DNA sequence where VDR might bind and then testing for its presence.

Feldman said it is uncertain whether VDR affects cells early in the process of becoming a fat cell, causing a final determination of brown or white to be made before the cell actually develops into a fat cell, or whether it is possible for white cells to later develop characteristics of brown fat cells if VDR becomes blocked.

Feldman and Malloy have already begun working on developing a therapy that would use some sort of small molecule to block VDR from inhibiting the production of the UCPI protein. The goal is to keep the VDR from blocking development of brown fat, but not interfere with the receptor’s ability to bind with vitamin D and engage in other processes it regulates, such as calcium homeostasis, Feldman said. “That’s what the utopian therapy would be.”

The researchers emphasized that even if the therapy they’re trying to develop proves effective, it would likely be years before it could be made available to the public.

They also point out that it will be important to compare the brown fat cells that are generated through this approach in the lab to those that are formed naturally in humans in order to understand whether there are differences.

This research was supported in part by a National Institutes of Health Doherty New Innovator Award and by the Child Health Research Institute at Stanford.

Stanford’s Department of Pediatrics also supported the work.
Gene decides whether to accept stem cells from same species

By Christopher Vaughan

To live together harmoniously in our bodies, cells need to be able to distinguish which of those among them are sanctioned residents and which are interlopers. This way, native cells can be left alone to do their jobs, and foreign cells can be attacked and removed.

The ability to identify friend from foe is made possible by the major histocompatibility genes, or MHC genes, which in humans and other vertebrates determine, for example, that a pregnancy is OK but organ transplants must be rejected (thus the need for immunosuppressants).

Now, researchers studying a marine organism called Botryllus schlosseri at Stanford’s Institute for Stem Cell Biology and Regenerative Medicine and Stanford’s Hopkins Marine Station have discovered a single gene that determines whether cells are accepted as self or destroyed by immune cells as non-self. The finding was published in Science.

Researchers studying a marine organism called Botryllus schlosseri have discovered that it has a single gene that determines whether cells are accepted as self or destroyed by immune cells as non-self. The finding was published in Science.

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a random process caused genetic drift.

The DNA sequences traced by the researchers were chosen because of the unique way they are inherited: the Y chromosome is passed only from father to son, and the mitochondrial genome is passed from a mother to daughter. This way, native cells can be left alone to do their jobs, and foreign cells can be destroyed by immune cells as non-self.

The tree also excluded all buffer phases, which are proxies for the periods of time between specific branching events. Bastamante and Poznik obtained highly accurate sequencing results over a length of about 10 mega-bases of Y chromosome DNA (or 10 million nucleotides) for each of the 69 individuals. They then estimated the yearly mutation rate on the Y chromosome by calibrating it with a known event: the human settlement of the Americas. They calculated that the first humans to reach the continent arrived 15,000 years ago.

Mutations shared by all Native Americans today must have occurred prior to the founding of the colonies, whereas many of those that vary among indigenous American populations arose during the past 15,000 years. They also calculated that the first people to reach the Americas and their relatives’ germ cells, said senior research scientist Ayedel Vooksoyobiny, PhD, a co-lead author of the study. To analyze the recently completed Y chromosome genome for the histocompatibility and evolutionary history of these sequences, the researchers applied sophisticated new algorithms for genetic analysis. These tools automatically identify new gene candidates and zero in on the needle in the haystack: the BHF gene itself, said postdoctoral scholar Aaron Newman, PhD, another co-lead author.

"This finding reveals a fusion-rejection system that is now understood to be shared among all vertebrates, including the actinopterygians, which are a group that represents a time when only a few sequences were passed on, and many died out due to an external event that’s not yet been identified. “For the most part, it’s a random process,” said Poznik.

Some lines die out, some are successful. But it’s also possible that there may be elements of that diversity that predispose these lineages to coalesce at certain times.

Elsewhere, the researchers sit on the advisory boards of several iSM projects, including the Siebel Stem Cell Institute and the Stem Cell Institute Genome Center; graduate student Winston Koh; research assistant Katherine Ishinaga; Gary Mantalas, Karla Palmeri and Lolita Penland; and former graduate student Christina Fan, PhD.

This study was supported by the National Institutes of Health, the Virginia and D.K. Ludwig Fund for Cancer Research, the Department of Defense, the Siebel Stem Cell Institute and the Thomas and Stacey Siebel Foundation.

Christopher Vaughan is communications manager for the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Carlos Bustamante

CIRES PRESS

"Previous research has indicated that the male MRCA lived much more recently than the female MRCA.

human demographic history that predispose these lineages to coalesce at certain times.

Several other Stanford researchers involved in the work include Marlene Jensen, PhD; Roy Herbst, PhD; research assistant Muh-Ching Yee, PhD; Ghia Euskirchen, PhD; director of the DNA Sequencing Program at the Center for Human Genome Research; professor of infectious diseases and computer science; and former graduate student Jeffrey Kidd, PhD; and senior research associate Peter Underhill, PhD.

The research was done in collaboration with scientists from Stony Brook University in New York, the University of Michigan in Ann Arbor, and the Institute Pasteur in Paris. It was funded by the National Library of Medicine, the National Science Foundation, the National Institutes of Health, the Institute Pasteur, the National Institutes of Health, the Fan, PhD; and the National Science Foundation and the Siebel Foundation Simon e Cino Deluca.

Several of the researchers sit on the advisory boards of have consulted for or own stock in 23andMe, Perso- nInc., iLeVate and Ancestry.com.

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**Young cancer survivor becomes top junior golfer**

12-year-old Grace Chen helps to raise money for leukemia research and treatment

**By Robert Dicks**

“It’s a relief that I can do what other kids do.” Grace Chen, 12, of Sunnyvale, Calif., was discussing how, since recovering from childhood leukemia, she can go to school, hang out with friends, watch TV — basically have a normal life. Well, mostly normal. There aren’t many other girls her age who can hit a golf ball 230 yards.

With 25 trophies scattered around her house, it’s obvious that Grace has the whole golf thing down. It’s been that way since she was 6 and in recovery from five years of treatment for acute lymphocytic leukemia, or ALL, at the Bass Center for Cancer and Childhood Blood Disorders at Packard Children’s Hospital.

“My wife, Ni, and I wanted her to start doing something that would help her physically and mentally,” said Grace’s father, Weixing Chen. “Team sports weren’t best because of the requirements for physical activity and the possibility of germs spreading between kids. So we figured golf — with open, fresh air and beautiful settings would be right for her, and she could do it in her own pace and get good exercise.”

Golf quickly became something more than just exercise for Grace. In its first year, she won seven medals in five categories in a national competition. Recently, she made her fifth annual trip to the U.S. Kids Golf World Championship at Pinehurst, N.C. Gary Dahl, MD, a physician at Packard Children’s, is not surprised.

“Grace represents a very important trend in leukemia treatments,” said Dahl, who also is a professor of pediatrics and of microbiology and immunology, was appointed the David and Susan Heckerman Professor, effective June 13.

In recognition of Pizzo’s service as dean of the School of Medicine from 2001 to 2012, and as a reflection of the high regard in which he is held, the school established a professorship in October 2012 with the intent that he be the first holder upon the end of his tenure as dean. The professorship was made possible by gifts from Susan and David Heckerman, PhD ’90, MD ’92; Stanford Hospital & Clinics; and Lucile Packard Children’s Hospital.

David Heckerman is senior director of the eScience Group at Microsoft Corp. Susan Heckerman has devoted her life to raising her children and charitable work. Groups she has worked with include Dechen Ling, the Open Window School and The Mirman School.

Yasser El-Sayed, MD, professor of obstetrics and gynecology and obstetrician-in-chief at Lucile Packard Children’s Hospital, was appointed the Charles B. and Ann L. Johnson Professor in the School of Medicine, effective June 13. El-Sayed also serves as director of the Division of Maternal-Fetal Medicine and Obstetrics.

The professorship was established in 1997 as part of a larger gift made by Charles and Ann Johnson to create the Johnson Center for Pregnancy and Newborn Services at Packard Children’s. The professorship is held by the chief of the Division of Maternal and Fetal Medicine, Ann Johnson received her MD from Stanford in 1977 and was a resident in psychiatry at Stanford Hospital from 1977 to 1980. She specializes in psychopharmacology. Charles Johnson is chair of the board of directors of Franklin Resources Inc., a San Mateo-based investment firm, and a member of the ownership group of the San Francisco Giants.

George Fisher, MD, PhD, professor of medicine, was appointed the Colleen Haas Chair in the School of Medicine, effective June 13.

Fisher, who also serves as director of the Cancer Clinical Trials Office, runs a research program that focuses on clinical trials for patients with gastrointestinal cancers.

The professorship was established in October 2011 with a gift from Robert Haas in honor of his wife’s birthday. Colleen Haas earned two degrees from Stanford, a bachelor’s degree in 1968 and a law degree in 1971. Robert Haas is an alumnus of UC-Berkeley and Harvard Business School. He served in the Peace Corps and as a White House Fellow prior to joining Levi Strauss & Co., where he served as CEO 1984-99 and chairman of the board from 1999 to 2007.

Matthew Scott, PhD, professor of developmental biology, genetics and of bioengineering, was appointed the Howard H. and Jessie T. Watkins University Professor, effective June 13.

Scott’s research focuses on how embryonic development is governed by proteins that control gene activity and signaling processes. He is exploring how defects in the regulators of development, or in related proteins, lead to birth defects, cancer and neurodegenerative disease.

The professorship was established from a bequest of Zoe Watkins Johnson in honor of her parents.

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**Researchers share $250,000 Alpert Prize for their work in genetics**

Ronald Davis, David Hogness and David Botstein are the 2013 Warren Alpert Foundation Prize for their seminal contributions to the creation of a human genetic map.

Davis, PhD, professor of genetics and of biochemistry; Hogness, PhD, professor emeritus of biology; and Botstein, PhD, who is now on the faculty of Princeton University and who previously held professorships at Stanford and MIT, will share the $250,000 prize and be honored Oct. 3 at a symposium at Harvard Medical School.

The researchers’ discoveries led to the identification of thousands of disease genes and helped to establish the framework for the Human Genome Project. The Alpert Prize recognizes researchers for basic discoveries that promise to improve human health.

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**Pizzo, El-Sayed, Scott appointed to endowed professorships**

Four School of Medicine faculty members were recently named to endowed professorships.

**Philip Pizzo, MD**, professor of pediatrics and of microbiology and immunology, was appointed the David and Susan Heckerman Professor, effective June 13.

In recognition of Pizzo’s service as dean of the School of Medicine from 2001 to 2012, and as a reflection of the high regard in which he is held, the school established a professorship in October 2012 with the intent that he be the first holder upon the end of his tenure as dean. The professorship was made possible by gifts from Susan and David Heckerman, PhD ’90, MD ’92; Stanford Hospital & Clinics; and Lucile Packard Children’s Hospital.

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