Use science to make world better, grads told

By Tracie White

Developmental biologist Lucy Shapiro, PhD, told 2015 graduates of the School of Medicine how, as a basic scientist who spent most of her life studying single-celled bacteria, she stepped out of her laboratory and onto the global stage to try to help the world avert a potential disaster.

“About 15 years ago, I sat up and looked around me and found that we were in the midst of a perfect storm, said Shapiro, the Virginia and D. K. Ludwig Professor, speaking at the school’s commencement June 13 on Alumni Green. “There was a global tide of emerging infectious diseases, rampant antibiotic and antiviral resistance amongst all pathogens and a poor to nonexistent drug pipeline.

For me the alarm bells went off, and I was convinced that I had to try and do something. Let me tell you the story of how I stepped out of my comfort zone. I launched a one-woman attack.”

She took any speaking engagement she could get to educate the public about antibiotic resistance; walked the corridors of power in Washington, D.C., lobbying politicians about the dangers of emerging infectious diseases; and used discoveries from her lab on the single-celled Caulobacter bacterium to develop new, effective disease-fighting drugs.

Bench-to-bedside for a better world

A recipient of the National Medal of Science, Shapiro exhorted the graduates to be unafraid of breaking out of their comfort zones and to use science to improve the human condition. Bridging the gap between the lab and the clinic can make the world a better place, she said.

Lloyd Minor, MD, dean of the School of Medicine, also emphasized the importance of bench-to-bedside work in his remarks to the graduates. There has never been a better time for shepherding advances in basic research into the clinic, he said.

“You are beginning your careers at an unprecedented time of opportunities for biomedical science and for human health,” he said.

This year’s class of 195 graduates comprised 78 students who earned PhDs, 78 who earned medical degrees and 39 who earned master’s degrees. It included Katharina Sophia Volz, the first-ever graduate of the Interdepartmental Program in Stem Cell Biology and Regenerative Medicine — the first doctoral program in the nation focusing on stem cell science and translating it to patient care.

Volz, whose work in the lab has opened the doors to improvements in clinical care for heart patients, said Stanford Medicine is the place to be for scientists who want to make a difference in the world.

“Everybody else is reaching for the stars. We can do the best work here of all.”

Departments in emergency medicine, biomedical data science to be created

By Ruth Schechter

In a move that reflects the changing landscape of health care and biomedicine, the Stanford University Board of Trustees has unanimously approved the creation of two new departments in the School of Medicine.

The Department of Emergency Medicine and the Department of Biomedical Data Science will be the school’s first new departments since the Department of Otolaryngology-Head and Neck Surgery was established in 2003.

“Bringing emergency medicine to full department status, and unifying biostatistics and bioinformatics under the new Biomedical Data Science Department gives us the opportunity to leverage our existing strengths in these disciplines and position ourselves for continued success,” said Lloyd Minor, MD, dean of the School of Medicine.

Creating departments dedicated to these disciplines will position Stanford as a leader in these fields, which will help to attract and retain the finest faculty, students and trainees, he added, as well as expand research and clinical programs that will bring exceptional care to patients.

The two new depart-ments established at the School of Medicine.

Some heartburn drugs may boost risk of heart attack, according to study

By Bruce Goldman

A large data-mining study carried out by investigators at the School of Medicine has linked a popular class of heartburn drugs to an elevated risk of heart attack.

Proton-pump inhibitors, or PPIs, are among the world’s most widely prescribed drugs, with $14 billion in annual sales. They are effective at lowering the acidity of the stomach, in turn preventing heartburn, a burning sensation in the chest that occurs when stomach acid rises up into the esophagus. In any given year, more than 20 million Americans — about one in every 14 — use PPIs such as omeprazole (trade name Prilosec) for heartburn, also known as acid reflux or gastroesophageal reflux disease.

“The association we found with PPI use and increased chances of a subsequent heart attack doesn’t in and of itself prove causation,” said the study’s lead author, Nigam Shah, PhD, MBBs, an assistant professor of biomedical informatics and assistant director of the Stanford Center for Biomedical Informatics Research. But, he said, the study combed through electronic health records of nearly 3 million people and crunched trillions of pieces of medical data, raising concerns that should be taken seriously, especially now that PPIs are available over the counter.

More than 100 million prescriptions are filled every year in the United States for PPIs, a class of drugs long considered benign except for people concurrently taking the...
In Kenya, program changes male attitudes about sexual violence

By Erin Digita1e

In Kenya, where rape and violence against women are rampant, a short educational program last- ing improvements in teenage boys’ and young men’s attitudes toward women, a study from the School of Medicine has found. The boys and men in the study also were more likely to try to halt violence against women after participating in the program.

The study was published online June 9 in the Journal of Interpersonal Violence.

The program was developed by No Means No Worldwide, a nonprofit, nongovernmental organization that works in the slums of Nairobi to prevent sexual assault on girls and women. Prior Stanford studies have shown that the group’s empowerment training for adolescent girls produces large reductions in the rate at which these girls are raped. The curriculum for males aimed to change attitudes that lead adolescent boys and young men to think it is acceptable to assault or rape their female peers.

“The curriculum for these young men is centered on getting them to think about what kind of people they want to be,” said lead author Jennifer Keller, PhD, clinical associate professor of psychiatry and behavioral sciences. “It’s about really getting them invested in why they need to step up and care about violence toward women. It affects their mothers, sisters and girlfriends.”

Understanding consent

The study included 1,543 males, ages 15-22, who were from Nairobi slums. At 29 high schools, 1,250 of them received six-two hour educational sessions from No Means No Worldwide. The intervention curricu-lum, called “Your Moment of Truth,” focused on helping them recognize the cultural normalization of violence against women, and gain skills and courage to speak out about sexual assault. Topics of discussion included myths about women, negative gender stereotypes, and when and how to safely intervene if you see someone else acting vio-lently toward a woman, and what constitutes consent and how to get that consent.

The comparison group of 293 boys and men at seven other high schools received Kenya’s usual two-hour life-skills class.

The researchers used anonymous surveys to ask the participants in both the experimen-tal and control groups about their attitudes toward women; their endorsement of rape myths; whether they had witnessed sexual harassment, physical threats or physical or sexual assault of women; and whether they had successfully intervened to stop such harass-ment, threats or assault. The boys and men in the experimental group completed surveys before the educational program began, immediately after it ended, and 4½ and nine months later. The participants in the comparison group completed surveys before receiving life-skills training and nine months later.

At the start of the study, participants in both groups reported negative views of women and agreement with myths about sexual assault, although the views of the control group were slightly higher than those of the experimental group, possibly because they were slightly younger. After the classes, the experimental group had more posi-tive views toward women and less belief in rape myths, and the improvement persisted 4½ and nine months later. The comparison group had unim-proved or worsened attitudes toward women at the nine-month follow-up.

Making an impact

Similar numbers of participants in both groups witnessed verbal harassment and physical or sexual assault of women, but the experimental group was at least twice as likely as those in the comparison group to successfully halt such assaults. Within the experimental group, participants with the most positive attitudes toward women were the most likely to step in.

“I’m very excited that this was done in Kenya, that even in this setting with high levels of violence toward women we were able to make such an impact,” Keller said.

Future studies will examine how boys’ and young men’s attitudes relate to their behavior in their own relationships, she said. “It’s harder to do,” Keller said, noting that research participants may not always admit, even anonymously, that they have behaved violently to-ward a girlfriend.

The study’s success with a relatively young group of males dovetails with prior research showing that it is easier to change negative gender stereotypes in younger groups, she added. In the United States, efforts to im-prove young men’s attitudes often come too late, but earlier intervention might work better, Keller said.

Other Stanford co-authors of the study are Neville Golden, MD, professor of pediatrics and chief of the Division of Adolescent Medicine at Lucile Packard Children’s Hospital Stanford; and Cynthia Kapphahn, MD, professor of pediatrics and an adolescent medicine specialist at Lucile Packard Children’s Hospital San-ford. Other collaborators included Jake Sinclair, MD, and Lee Paiva, co-founders of No Means No World-Wide, and collaborators at United States International University, in Nairobi; at the nonprofit NGO Ujamaa-Africa; and at Edgework Consulting in Boston. The study was funded by Ujamaa-Africa.

Stanford’s Department of Pediatrics also supported the work.

Gene discoveries may lead to regeneration of cells needed for hearing

By Jeffrey Norris

School of Medicine scientists have discovered biological mechanisms that appear to play a role in the regeneration of cells in the inner ear.

Over a lifetime, these cells often are damaged or die due to oxidative stress, excessive noise exposure or toxic drugs. The accumulated loss can significantly compromise hearing. Nearly one in four people ages 65-74, and half who are 75 or older, are candidates for hearing aids because of disabling hearing loss.

The discoveries could lead to new ways of evaluating, in animal models, experimental drug treatments intended to prevent hearing loss or restore hear-ing, and might even lead to methods for regenerating vital cells that have been lost, said Stefan Heller, PhD, professor of otolaryngology.

A paper describing the findings, as well as new methods to quickly link changes in cell function during development to molecular changes within cells, was published June 9 in Cell Reports. Heller is the senior author of the paper.

Postdoctoral scholars Jörg Waldhaus, PhD, and Robert Durruthy-Durruthy, PhD, share the lead authorship.

Sound waves striking the eardrum cause vibrations that are transmitted through tiny bones in the middle ear to fluid within the snail-shell-shaped cochlea of the inner ear. Specialized cochlear cells in a region called the organ of Corti use hairlike sensors to detect the vibrations in cochlear fluid and then trigger nerve signals that are sent to the brain.

“Compared to other senses, we know very little about how hearing works,” Heller said. “The sense of touch is so rare. We have to crack open a bone to get to them. They perish quickly, so we must work fast.”

The researchers identified more than 2,000 hair cells in a mouse ear, Heller said, but only 3,200 hair cells in a mouse ear. Using new techniques to rapidly and deeply probe individual cells, Helle-r’s team has begun to close the knowledge gap.

Molecular mysteries

Many of the biophysical properties of hair cells are understood. Different hair cells along the cochlear spiral are tuned to respond to distinct ranges of sound frequency based on differences in their electrical properties. Frequency is encoded by the place and properties of the cells’ locations in the cochlea. This understanding has led to the develop-ment of cochlear implants to restore hearing in deaf people.

However, little is known about the molecular biology that determines how hair cells develop at specific locations and how different electrical properties arise among hair cells specialized to detect different frequencies. This makes it difficult for scientists to envision strategies that might be used to regenerate hair cells or to prevent their death, particularly in the high-frequency region of the co-chlea, where cells are more susceptible to injury.

Discoveries by Stefan Heller and his colleagues could lead to new ways of evaluating, in animal models, experimental drug treatments intended to prevent hearing loss or restore hearing.

INSIDE STANFORD MEDICINE
**Discovery of molecular pathway could lead to pancreatitis treatments**

**By Tracie White**

The pancreas is a tricky organ for researchers and surgeons alike because of its sensitivity. Tucked away in a hard-to-reach spot behind the stomach, it’s in charge of secreting enzymes to help digest everything you eat. Even slightly puncturing the pancreas during surgery can cause it to begin digesting itself.

That may be ironic because there is so little understanding of what causes pancreatitis, a fairly common and quite painful disorder.

“We try not to touch the pancreas,” said Aida Habtezion, MD, assistant professor of gastroenterology and hepatology. “That’s one of the reasons the field has not progressed much. We don’t have much access to the pancreas. We basically don’t want to touch it when it is inflamed with pancreatitis.”

By working with animal models and cells retrieved from the few surgeries involving the human pancreas, Habtezion has spearheaded new research that provides insight for the first time into the molecular pathway that leads to chronic pancreatitis, the debilitating, long-term inflammation of the organ.

In a study published May 18 in *Nature Communications*, Habtezion and her colleagues found that blocking this pathway stops the progression of the uncontrolled growth of scar tissue, or fibrosis, that’s the hallmark of chronic pancreatitis.

“This is the first step to showing that you can alter the progression of this disease,” said Habtezion, senior author of the study. The lead author is postdoctoral scholar Murali Muralidhara, MD.

Habtezion, a gastroenterologist with a background in immunology, splits her workdays between the lab and the hospital. Her interest in these patients has crossed over into her lab.

“Acute pancreatitis is one of the most common gastrointestinal admissions-related illnesses,” she said. “Some people just have one or two episodes, and we never see them back.” Others go on to develop chronic pancreatitis, which is a risk factor for pancreatic cancer.

**No known cure**

Chronic pancreatitis is marked by constant, severe stomach pain. There is no known cure and little treatment beyond narcotics to help control the pain. The disease destroys the ability of the pancreas to absorb nutrients, leading to nutritional deficiencies and malnutrition, along with the crippling nausea and diarrhea caused by the abdominal pain. Key contributors to the disease include excessive alcohol consumption, gallstones and genetic factors.

“My lab has been interested in the inflammatory responses associated with pancreatitis and in understanding the molecular pathways that may be targeted to alter the progression of the disease,” Habtezion said. It’s generally understood that chronic pancreatitis is marked by the uncontrolled growth of scar tissue in the pancreas, slowly destroying the organ’s ability to function. Just how this happens is less clear.

In previous research, Habtezion’s lab has shown that macrophages, a type of immune cell in the body, play a role in the acute form of pancreatitis. The goal of the new study was to determine the role of macrophages in the development of chronic pancreatitis from the acute form of the disease. Previous research has shown that pancreatic stellate cells may play a role in fibrosis. These cells live in the pancreas and travel to injury sites when activated.

Next, they set out to determine if blocking this pathway would slow or stop fibrosis. This is where colleagues from Cedars-Sinai Medical Center — co-authors Stephen Pandol, MD, director of basic and translational pancreas research, and Ramachandran Murali, PhD, associate professor of biomedical sciences — helped out.

“Our most important finding was that there is cross-talk between macrophages and stellate cells,” Habtezion said. “We identified this pathway.”

Next, they looked at how to use this knowledge to develop a drug to halt fibrosis.

“When it comes to drug development, we aren’t at the point where this pathway would slow or stop fibrosis,” Dallas said. “It’s too early to say exactly how these drugs work.”

The new research, published May 18 in *Nature Communications*, has implications for the development of a drug for chronic pancreatitis and for other fibrotic diseases.

**New research provides insight for the first time into the molecular pathway that leads to chronic inflammation of the pancreas.***

*This illustration from the spring 2014 issue of Stanford Medicine magazine won a silver award from CASE.*

By Susan Ipakitichan

Stanford Medicine magazine earned six awards, including prize-winning stories on "best articles of the year," in a national competition.

In all, the magazine took home a platinum, three golds, a silver and a bronze in the 2015 Circle of Excellence awards held by the Council for the Advancement and Support of Education, or CASE. The magazine is produced by the medical school’s Office of Communications & Public Affairs.

Writer Tracie White earned the sole platinum award in the best-articles category for “Almost without hope,” a look at the heartbreaking scarcity of medical resources on an Indian reservation in South Dakota. The judges wrote that they “admired the author’s handling of a subject ripe with standard conventions and hackneyed writing. The author never fell into this trap, capturing the story and delivering it creatively. With a strong formative voice, the author got this one right. Job well done.”

Stanford Medicine earned a gold award in the special-consumership magazine category. One judge described her as “a storyteller who can draw the reader in.” Judges added that “the writing makes the technical and medical topics understandable to lay readers.” The magazine is edited by Rosanne Spector.

The magazine also earned its fourth consecutive gold award in the special-education staff writing category. Following are the five stories submitted in this category:

- "Immune system disruption," by Kris Newby, tells the story of a young woman felled by chronic fatigue syndrome who is now recovering and taking part in a trailblazing Stanford study.
- "Fresh starts for hearts," by Krista Conger, describes the potential for stem cell research to help patients, such as the children in one family stricken by a life-threatening heart disease.
- "It's generally understood that chronic pancreatitis is marked by the uncontrolled growth of scar tissue in the pancreas, slowly destroying the organ's ability to function. Just how this happens is less clear." The author got this one right.
- "Rethinking Alzheimer's," by Bruce Goldman, captures the advances in research into the disease.
- "Brain attack," by Erin Digutale, focuses on a controversial psychiatric disease that devastates children's lives.

The judges said they were "particularly blown away by the depth of the reporting and the degree of access the reporters had to their sources."

The magazine earned a gold award for periodical design for its spring 2014 issue, whose theme was "on the cutting edge of science." The judges said the theme was "carried through the entire magazine in an exceptional way, and we especially loved the variety of interpretative pieces that fit into the theme in the illustrations, each of which was compelling, a wonder to look at and the greater acceptance of women in the field.

The magazine won third place in the "consumer (small)" category, which includes stories in magazines with a circulation of less than 500,000, in the association’s 2014 contest. The annual contest is open to print and broadcast reporters throughout the country and recognizes the best health reporting. More than 420 entries were received for this year’s contest.

**School’s magazine draws top awards in national competition**

**By Tracie White**

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**Magazine article nabs award in health-care journalism contest**

“Opening up: The evolving world of surgery,” an article published in the summer 2014 issue of Stanford Medicine magazine, won an award from the Association of Health Care Journalists.

Written by R Putman Richter of the medical school’s Office of Communication & Public Affairs, the story describes the experience of a sixth-year surgical resident at Stanford to illustrate changes in surgical practice and training and the greater acceptance of women in the field.

The article won third place in the “consumer (small)” category, which includes stories in magazines with a circulation of less than 500,000, in this year’s contest. The annual contest is open to print and broadcast reporters throughout the country and recognizes the best health reporting. More than 420 entries were received for this year’s contest.

**New research provides insight for the first time into the molecular pathway that leads to chronic inflammation of the pancreas.***

*This illustration from the spring 2014 issue of Stanford Medicine magazine won a silver award from CASE.*

By Tracie White
By Jennifer Huber

Researchers at the School of Medicine have determined that toothed whales lack functional Mx genes—a surprising discovery, since all 56 other sequenced mammals in the study possess these genes to fight off viruses like HIV, measles and the common cold.

Modern toothed whales, including dolphins, orcas and sperm whales, have inherited defunct copies of the Mx1 and Mx2 genes, potentially altering their immune systems. The basic role of these Mx genes is to make proteins that fight viral infections, and researchers suspected that understanding this newly discovered mysterious genetic anomaly will help prevent certain cancers as they face exposure.

"Given how important the Mx genes seem to be in fighting off disease in humans and other mammals, it’s striking to see a species lose them both and go about its business for millions of years," said Geer Bejerano, PhD, associate professor of developmental biology, of computer science and of pediatrics. "It’s hard to determine if that’s related to the die-offs. We hope that our observations will provide particular targets to go after when cures are found, so we can better understand what is happening,” Bejerano is the senior author of a published online June 22 in Proceedings of the National Academy of Sciences, that describes the work. The lead author is graduate student Benjamin Braun.

Double-pitched strategy

Bejerano said his lab was investigating Mx genes because, in primates, they are engaged in an arms race against rapidly evolving viral proteins. In order to determine the evolutionary genomic difference observed between the toothed and baleen whales, they share a common ancestor. In the toothed whales, baleen whales have plates, which they use to filter food from water.

"The simplest, most likely scenario is that these inactivating mutations are common in the toothed whales that lost both Mx genes shortly after the baleen whales and toothed whales split about 33-37 million years ago,” Bejerano said. "It’s tempting to think that this common ancestor was subjected to a very nasty virus that was exploiting the Mx1 and Mx2 genes. Their option was to lose both genes or die. We can’t know for sure, but it’s a tempting hypothesis based on how some viruses seem to exploit Mx genes today.”

Bejerano hopes these observations will inspire other researchers to collect samples and do in vitro experiments to determine whether the toothed whales’ immune systems are compromised or whether they've instead developed intriguing compensatory mutations. Ultimately, this understanding may help scientists fight human diseases, such as autoimmune disorders.

"It’s likely that the toothed whales’ immune system is very different from ours,” Bejerano said. "I think this will open up very exciting research avenues, either to better protect the compromised genes, or to study their different viral defenses, and someday add them to our own arsenal. We’re putting the genomic discovery out there, and I hope immunologists will follow up on it.

"Every single genome sequenced is a treasure trove of secrets. This is an amazing time to be a thoughtfull genomics refract. And hopefully, we’ve helped make it a slightly better time to be a toothed whale,” Bejerano said.

Other Stanford co-authors of the study are postdoctoral scholar Amir Marcovitch, PhD, former postdoctoral scholar Gray Camp, PhD, and former undergraduate student Robin Jia.

The research was supported by a Stanford Center for Computational, Evolutionary and Human Genomics postdoctoral fellowship, a Stanford School of Medicine Dean’s postdoctoral fellowship, a PhRMA Foundation Informatins postdoctoral fellowship, a Microsoft Research Faculty Fellowship, the David and Lucile Packard Foundation and the National Institutes of Health. Stanford’s Department of Computer Science, Department of Developmental Biology and Department of Pediatrics also supported the work. on

Jennifer Huber is a freelance writer.

Toothed whales have survived millions of years without key antiviral proteins

By Bruce Goldman

A new study by researchers at the School of Medicine found that synchronized physiological interactions between remote brain regions have genetic underpinnings. The research was performed at Stanford but was made possible by collaborations with the Seattle-based Allen Institute for Brain Science and the IMAGEN Consortium, a multicenter European project. The study’s author, Bruce Goldman, PhD, is an associate professor of neuroscience.

"Genes are used to make RNA and, from there, to make proteins," Bejerano said. "So we obtained RNA samples from two toothed whales, a baleen whale and two closely related species. When we looked at the output — the RNA that the genes were trying to make — there was nothing like a functioning Mx RNA coming out of these messed up gene loci in the toothed whales.

"In rest-state fMRI scans, the individual is asked to simply lie still and relax for several minutes. The results of these scans indicate that even at rest, the brain’s functional networks continue to hum along at their own distinguishable frequencies and phases, like different radio stations playing simultaneously, but quietly, on the same radio.

Digging into fMRI images

However, whether resting-state fMRI-derived images, which measure local blood flows in different places throughout the brain, actually reflect neuronal activity has been controversial.

"There’s been some skepticism regarding the validity of resting-state network activity," said Greicius. "We wanted to dig deeper and get to the molecular underpinnings of these imaging results, indicating that the brain maintains its exquisite functional-network architecture even at rest."

To start, Greicius and his colleagues conducted whole-genome sequenced toothed whale data to elucidate the three-dimensional nature of neural circuits. The investigators were hunting specifically for a set of 136 genes that showed a correlated pattern of expression across dozens of brain areas. Using sophisticated statistical methods, they identified a set of 136 genes that shared a correlated pattern of gene expression in regions within each network.

These 136 genes were not specific to any single network, Greicius noted. Rather, “any one of these genes that was being expressed at a high, intermediate or low level in one region of any network, regardless of which network you’d picked, was also being expressed at corresponding levels in the other regions of that network,” he said.

The Stanford team validated their findings by turning to another database. The IMAGEN Consortium has conducted widespread fMRI studies and has been collecting data at different times in the life span of each individual. Because the toothed whale is a long-lived species compared to humans, the researchers could use the data from the first time point to validate findings from the second.

By comparing the two sets of data, the team was able to confirm that the patterns of gene expression observed in toothed whale brain tissues during rest were not an artifact of the toothed whale’s long lifespan, but rather a key feature of the brain’s functional organization.

Researchers are currently testing 136 genes within five different groups of brain areas, looking for differences in expression levels. "So far, we’ve seen differences in gene expression between different brain regions in both ‘healthy’ and ‘ill’ toothed whales. And hopefully, we’ve helped make it a slightly better time to be a toothed whale,” Bejerano said.

Other Stanford co-authors of the study are postdoctoral scholar Philip Sabatini, MD, PhD, and former postdoctoral fellow Aarti Shah, PhD. Stanford’s Department of Computer Science, Department of Developmental Biology and Department of Pediatrics also supported the work. on

Jennifer Huber is a freelance writer.

Genetic underpinnings of brain networks seen in imaging study

By Michael Greicius

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Men are not the only ones who have prostate cancer. In fact, more than 10,000 women are diagnosed with prostate cancer each year. As a result, many women are not aware that they are at risk for the disease. This can lead to delays in diagnosis and treatment, which can ultimately affect their quality of life.

The National Institutes of Health (NIH) is currently funding a study to evaluate the effectiveness of a new blood test for detecting prostate cancer in women. The test, called the Prostate-Specific Antigen (PSA) test, is already used to screen men for prostate cancer. However, the test is not yet approved for use in women.

The study is called the PROSE Study, which stands for Prostate Cancer in Women: Efficacy and Natural History. The study is being conducted at several hospitals across the country, including the NIH Clinical Center in Bethesda, Maryland.

The study will recruit 500 women who have been diagnosed with prostate cancer. The women will be randomly assigned to receive either the standard of care or an experimental treatment. The experimental treatment will involve the use of a new blood test to detect prostate cancer in women.

The study aims to determine whether the new blood test is effective in detecting prostate cancer in women. The study will also evaluate the safety and tolerability of the experimental treatment.

The results of the PROSE Study will help to advance our understanding of prostate cancer in women. The study will also help to inform future research and treatment options for women with prostate cancer.

The study is expected to last for several years. Participants will be followed for up to 10 years after the study begins. The study is expected to enroll all women who meet the eligibility criteria and are willing to participate.

The PROSE Study is an important step in the development of new treatments for prostate cancer in women. The study will help to advance our understanding of the disease and improve treatment options for women with prostate cancer.

The study is being funded by the National Cancer Institute (NCI) and the National Institutes of Health (NIH). The study is being led by Dr. Andrew Tendick, a urologist at the NIH Clinical Center.
Graduation continued from page 1

Anywhere,” said Volz, 28, a native of Ulm, Germany, the birthplace of Albert Einstein. She has worked in 10 different labs across the globe. Her father and mother, Johannes and Luise Volz, traveled from Germany to celebrate.

“I’ve never been in a more supportive environment,” said Volz, who discovered the progenitors to the muscle layer around the coronary arteries, a finding with implications for regenerative medicine and finding treatments for coronary artery disease.

Well-wishers, garlands and fuzzy babies

Some in the crowd of well-wishers, seated under a giant white tent, held garlands of flowers for the graduates, while toddlers ran around the lawn and babies fussed and cried. The two student speakers added humor and pathos to the occasion, with memories of their years at Stanford.

“I’d like to run one last experiment,” said Francisco Jose Emilio Gimenez, a PhD graduate in biomedical in-

Lucy Shapiro, left, addresses graduates at the School of Medicine’s diploma ceremony on June 13. Monica Emerit-Wiener, who earned a medical degree, hugs her mother Gloria Emerit.

she was both nervous to be in front of the crowd and concerned about whether her fluffy black graduation cap would stay put. “I’m wearing a French pastry hat and worried it’s going to fall off,” she said.

Her years of education to become a physician changed the day she entered clinical care training. “From the day we started clinics, we would really never be the same as those bright-eyed individuals who gathered here for orientation,” she said. “How could we be after gaining such privileged access into the human condition?”

Role as government adviser

Shapiro’s desire to improve the human condition led her out of the lab to the nation’s capital. She has served in advisory roles in the administrations of Bill Clinton and George W. Bush on the threat of infectious disease in developing countries. Now director of the Beckman Center for Molecular and Genetic Medicine at Stanford, Shapiro has been a faculty member since 1989. She was founding chair of the Department of Developmental Biology and also started a biotech company in Palo Alto to test and develop antibiotics and antifungals.

Her lab at Stanford made breakthroughs in understanding the genetic circuitry of single-celled organisms, which is key to the future of global health.

“This is no ordinary time, from shattering political unrest in the Middle East and North Africa and the consequent flood of immigrant populations that serves as a petri dish for infectious pathogens, to global shifts in urban environments, to climate change, which is having substantial impact on health ... all contributing to the appearance of old pathogens in new places and new pathogens for which we have no immunity.

“We here must care about an Ebola outbreak 8,000 miles away in West Africa; we here must care about a cholera outbreak in Haiti; we wait for the consequences of the earthquake in Nepal. We live in a global village.”

This is your time to shape the future, Shapiro told the graduates.

“Step out of your comfort zone and follow your intuition,” she said. “Don’t be afraid of taking chances. Ask, ‘How can I change what’s wrong?’

At the School of Medicine’s commencement June 13, more than two-dozen faculty members, staff and trainees, as well as a student, were recognized for outstanding work in education or patient care, or both.

In addition, JOSEPH LIPSICK, MD, PhD, professor of pathology and of genetics, received one of the four 2015 Waber J. Gores Awards, the university’s highest teaching honor, at the university’s commencement June 14.

AWARDS IN MEDICINE

STEVEN LIN, MD, clinical instructor of medicine; KALPANA NATHAN, MD, clinical assistant professor of psychiatry and behavioral sciences; and IAN NELKIRAN, MD, MPH, clinical instructor of medicine, received the Arthur L. Bloomfield Award in Recognition of Excellence in the Teaching of Clinical Medicine.

GERALD GRANT, MD, associate professor of neurosurgery, received the Franklin C. Ellbaugh Jr. Award for Excellence in Advising Medical Students.

JOANNA BADGER, MD, clinical associate professor of dermatology, received the Alwin C. Rambar-James BD Mark Award for Excellence in Patient Care, which recognizes a member of the medical faculty for compassion in working with patients and their families, excellence in providing medical treatment, and effectiveness and pleasantness in interactions with patient-care staff.

ANDREW CONNOLLY, MD, associate professor of pathology, received the Lawrence H. Mathers Award for Exceptional Commitment to Teaching and Active Involvement in Medical Student Education.

NEIL GESUNDHEIT, MD, MPH, professor of medicine, received the Award for Excellence in Promotion of the Learning Environment and Student Wellness.

LUIGI GUO, an administrative associate in the Department of Pathology, received the Medical Education Staff Service Award.

DARREN SALMI, MD, clinical assistant professor of surgery and of pathology, received the Outstanding Lecture/Presentation Award.

NANCY CUNA, MD, received the Outstanding Community Clinic Preceptor—Clinical Instruction Award.

ERIKA SCHILLINGER, MD, clinical associate professor of medicine, received the Henry J. Kaiser Family Foundation Award for Excellence in Clinical Teaching.

GILBERT CHU, MD, PhD, professor of medicine and of biochemistry; TINA COWAN, PhD, associate professor of pathology; and SAKTI SRIVASTAVA, MD, associate professor of surgery, received the Henry J. Kaiser Family Foundation Award for Excellence in Preclinical Teaching.

YOSHII MITARAI, MD, clinical assistant professor of surgery; REBECCA COHEN, MD, clinical assistant professor of pediatrics; and MONICA STEMMLE, MD, clinical assistant professor of pediatrics, received the Henry J. Kaiser Family Foundation Award for Excellence in Clinical Teaching.

Two medical residents, KEVIN CHI, MD, pediatrics; VICTORIA KLYCE, MD, emergency medicine; JOZEFS LAZAR, MD, dermatology; RUSTIN MASSOUDI, MD, urology; FELIPE PEREZ, MD, anesthesiology, perinatal and pain medicine; and NINA VASAN, MD, psychiatry and behavioral sciences, received the Arnold P. Gold Foundation Award for Humanism and Excellence in Teaching.

The award is given to residents based on their commitment to teaching and the compassionate treatment of students, colleagues and patients and their families.

AWARDS IN BIO SCIENCES

KEVIN GRIMES, MD, MBA, associate professor of chemical and systems biology; and JULIE THERIOT, PhD, professor of biochemistry and of microbiology and immunology, received the Faculty Award for Excellence in Mentoring and Service.

MIIRIAM GOODMAN, PhD, associate professor of molecular and cellular physiology, and JOSEPH LIPSICK, MD, PhD, professor of pathology and of genetics, received the Faculty Award for Excellence in Diversity and Inclusion.

This award recognizes faculty who make distinguished contributions toward enhancing the quality of training and the educational experience for bio-sciences graduate students.

STEVEN SLOAN, MD/PhD student, received the Teaching Assistant Award.

SONG AWARD

Lipsick, who received a Waber J. Gores Award on June 14, was honored “for his deep commitment to improving the Cancer Biology Program curriculum as director of the program, revamping core courses in his sabbatical year, and including undergraduate as well as graduate courses.”

He was commended “for his dedication to undergraduate education — he was one of the first faculty to volunteer and develop a new course for Thinking Matters” and “for his generosity in mentoring his graduate teaching fellows, providing them opportunities to design and give lectures on topics of interest.”

Lipsick also was honored “for his thought-provoking courses that students described as ‘challenging, but SO fun. They are like puzzles! … Do your brain a favor and TAKE THIS course — they are like puzzles!’”

At the Henry J. Kaiser Family Foundation Award for Democracy in Teaching.

GORES AWARD

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At the Henry J. Kaiser Family Foundation Award for Democracy in Teaching.
Heartburn continued from page 1

Nigar Shah has pioneered the use of data-mining techniques to capture sometimes elusive but medically important phenomena.

Nicholas Leeper, MD, the study’s senior author and an assistant professor of vascular surgery and of cardiovascular medicine.

No elevated risk linked to H2 blockers

Interestingly, another commonly prescribed heartburn drug class called H2 blockers showed no association with heart attack risk, even among those who have been around longer than PPIs, are reason-ably effective against heartburn and are the second-largest selling class of drugs used to treat it.

The study’s findings lend support to an explanation for an unwise trend of using PPIs on heart-disease risk proposed by Stanford scientists a few years ago. Research done then showed that PPIs impede the pro-duction of an important substance, nitric oxide, in the endothelial cells that line all of the nearly 100,000 miles of blood vessels in the body. Shah has pioneered the use of data-mining tech-niques to capture sometimes elusive but medically important phenomena.

Arguing that a single department will allow us to ap-proach data and information in a whole new way, Altman, a member of the core planning group that prepared the pro-

Here’s what the study found:

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niques to capture sometimes elusive but medically important phenomena.
**Molecular cause of heart condition identified by researchers**

By Krista Conger

In 2012, researchers at the School of Medicine showed that heart muscle cells made from the skin of people with a cardiac condition called dilated cardiomyopathy had less force than those from people with a healthy heart. These cells also responded less readily to the waves of calcium that control the timing and strength of each contraction.

Now, the same research team has teased apart the molecular basis for these differences and identified a drug treatment that at least partially restores function to heart muscle cells from people with dilated cardiomyopathy. They also observed how a key heart signaling cascade, called the beta-adrenergic pathway, develops as heart muscle cells mature and how this function changes in both normal and diseased cells.

The researchers hope that the findings will help clinicians better hone their treatment protocols for a variety of cardiac conditions, which are now often treated with a one-size-fits-all approach.

“Right now, nearly all patients with cardiomyopathy are given drugs to modulate the beta-adrenergic pathway in the heart, which is known to be dysfunctional,” said Joseph Wu, MD, PhD, director of Stanford’s Cardiovascular Institute. “But we have little know what exactly is going wrong with this pathway at a molecular level.”

A paper describing the research was published online June 18 in Cell Stem Cell. Wu, a professor of medicine and of radiology, is the senior author of the paper, and postdoctoral scholar Haodi Wu, PhD, is the lead author. (Joseph Wu and Haodi Wu are not related.)

**Using skin-derived cells to study disease**

The research relies on what’s known as induced pluripotent stem cells, or iPS cells, to make heart muscle cells from skin. iPS cells can be coaxed to develop into nearly any tissue in the body. The technique gives researchers access to a variety of human cell types, such as brain and heart muscle cells, that are typically difficult to obtain for study.

The approach adds to others suggesting that heart muscle cells made from skin cells accurately incorporate the minute details of diseases that afflict those from whom the skin cells were derived.

“We wanted to characterize the mechanisms that underlie the functional impairment of the cells,” said Haodi Wu. “Until now, we’ve used iPS-cell-derived heart muscle cells as a disease model for cardiomyopa-thy, but it’s not been known how precisely these cells recapitulate the disease phenotype. Now we have shown that although normal and healthy cells undergo a similar development- al and maturation process, the mutation carried by the diseased cells causes them to lose the ability to pump blood effi- ciently. Eventually, the enlarged muscle weakens and fails, resulting in either heart failure, transplantation. Dilated cardiomyop athy can be due to restrictions in blood flow (a condition known as ischemia) that can cause a heart attack, or to nonischemic causes such as viral infection. Although many cases of non-ischemic dilated cardiomyopathy occur sporadically and without an apparent cause, dilated cardiomyopathy may be inherited through changes in the number of genes or the way those genes function. One of these mutations affects a protein called TNNT2, which is located on the muscle fibers of the heart and helps to regulate their contraction.

The researchers were building upon a 2011 study from the Wu lab published in Science Translational Medicine showing that stem-cell-derived heart muscle cells from people with dilated cardiomyopathy differed in obvious ways from those derived from healthy people. They contrast less forcefully and respond less strongly to the beta-adrenergic signal that increases heart rate and stroke force in response to stress or exercise.

**Molecular messengers degraded**

Haodi Wu and his colleagues showed that mutated TNNT2 in the cells from patients with dilated cardio myopathy changes the signaling by the muscle cells and stimulates chemical tags like methyl groups to attach to DNA and DNA packaging protein complexes called histones. This process is called epigenetic modification. These modifications work to increase the expression of two genes encoding proteins called phosphodiesterases, which degrade the molecule that transmits the beta-adrenergic signaling pathway.

To test their findings, the researchers stimulated heart muscle cells from patients with isoproterenol, which activates the beta-adrenergic pathway. Healthy cells responded vigorously, contracting about 80 percent more quickly and with about 60 percent more force. In contrast, the contraction rate of the diseased cells only increased by about 37 percent, and the force of the contraction remained roughly the same.

“The beta-adrenergic pathway is a key pharmacological target for many cardiac conditions. This study confirms that iPS-cell-derived cardiomyocytes can help us to understand biologically important pathways at a molecular level, and possibly distinguish a patient’s own heart cells for study is the epitome of personalized medicine.”

Other Stanford co-authors are postdoctoral scholars Mingxia Gu, PhD, Feng Lan, PhD, and Jared Churko; cardiovascular medical fellow Karim Sallam, MD; research associate Elena Mata, PhD; graduate students Anu Sharma; and senior research scientist Joseph Gold, PhD.

The work was funded by the American Heart Asso ciation and the National Institutes of Health.

Stanford’s Department of Medicine and the Stanford Cardiovascular Institute also supported the work.

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**$9 million grant establishes open-access autism database**

Dennis Wall, PhD, an autism re searcher at the School of Medicine, is leading a new project to establish the largest-ever collaborative, open-access repository of bioinformatic data on autism.

The Hartwell Autism Research and Technology Initiative, known as iHART, will provide the scientific com munity with a centralized repository of data to benefit biomedical research on autism and help children affected with the developmental disorder, which hinders social and communication skills. It is a $9 million grant from the Hartwell Foundation, a charitable organization whose mission is to support early-stage bio medical research projects that improve the health and well-being of children in the United States.

Wall, an associate profes sor of systems medicine in the Department of Pediatrics, will direct the iHART cloud-based computing and communica tions technology project. The initiative seeks to assemble a compre hensive scientific repository of data on autism spectrum disorder to help researchers develop new treatments for autism.

“The quest is to create a shared database that researchers can access anywhere on any mobile device or computer, serving as a central repository for autism research data,” Wall said.

The platform will enable research ers to ask questions that simulta neously draw on many kinds of data on autism spectrum disorder, including phenotypes, proteomics, metabolomics, genomics, measurements and imaging of brain activity, information from cell culture, microbe, blood-based biomarkers, physician narratives, diagnostic test results and treatment proto cols. The platform will include a portal to enable data integration, as well as experimental design and validation. The ini tiative will study single genetic, phenotypic, and other data on nearly 5,000 individuals affected with an autism spectrum disorder.

In addition to the School of Medi cine, the Hartwell Foundation will col laborate with the Stanford Bioinformatics Program, the Department of Pediatrics and the Department of Computer Science at Stanford, the Simons Foundation, the Simons Autism Research Initiative, the New York Genome Center, the University of California-Los Ange les and the New York Genome Center to accelerate the addition of autism data to the database.

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**Hearing continued from page 2**

Once hair cells die in a mature mammal, they are not replaced. But scientists have recently determined that a supporting cell type, called the inner pillar cell, has potential to regenerate hair cells in newborn mice.

In its new study of 2-day-old mice, Heller’s lab measured the activ ity of 192 genes. The researchers deter mined which genes were turned on, or “expressed,” in each of 808 hair cells and supporting cells from either the apex or base of the organ of Corti. They quanti fied this gene expression by measuring the amount of RNA produced from each gene.

The researchers identified patterns of gene expression that may determine whether inner pillar cells can give rise to new hair cells. Similarly, they discovered gradual changes in the expression of specific genes across cells that span the organ of Corti from its base to its apex that may correspond to how the establishment and main tenance of a population of hair cells responds to a range of sound frequencies.

**Crunching the data**

Using powerful number-crunching software to analyze the large amount of genetic data, Heller’s lab team accurately identified the two known types of hair cells, each with seven known types of supporting cells and created a computer-generated map of their locations within the organ of Corti. They did this using only the genetic data, but then used other pre viously known DNA sequences to inde pendently verify the accuracy of the cell identification and mapping.

The strategy the researchers used to project the spatial organization of cells within the organ of Corti from gene-expression data also should prove useful to biologists who study other types of cells in different organs, Heller said.

Rapid advances in single-cell gene expression research are likely to sup plant a standard technique called in situ hybridiza tion, according to Heller. The stand ard technique relies on labeled genetic probes to target individual genes one by one in order to identify specific cell types. The new approach of measuring hun dreds of genes in parallel and recon structing the organs in the computer appears to be much quicker.

“Molecular gradients play a key role in developmental biology, but in the past researchers had to sequence ten grad ients in one molecule at a time,” Heller said. “With these new techniques, we are identifying cells that, for example, have more expression of stem cells, cells that are analyzing the expression of many genes all at once, and we know precisely where they are.”

The research was funded by the National Institutes of Health, the Stanford Institute for Stem Cell Biology and Regenerative Medicine, the Hearing Health Foundation’s Hearing Restoration Project.

Jeffrey Norris is a freelance writer.

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