Skin cells of infertile men used to create sperm precursors

By Krista Conger

Stem cells made from the skin of adult, infertile men yield primordial germ cells — cells that normally become sperm — when transplanted into the reproductive system of mice, according to researchers at the School of Medicine and Montana State University.

The infertile men in the study each had a type of genetic mutation that prevented them from making mature sperm — a condition called azoospermia. The research suggests that the men with azoospermia may have had germ cells at some point in their early lives, but lost them as they matured to adulthood.

Although the researchers were able to create primordial germ cells from the infertile men, their stem cells made far fewer of these sperm progenitors than did stem cells from men without the mutations. The research provides a useful, much-needed model to study the earliest stages of human reproduction.

“We saw better germ-cell differentiation in this transplantation model than we’ve ever seen,” said Renee Reijo Pera, PhD, former director of Stanford’s Center for Human Embryonic Stem Cell Research and Education. “We were amazed by the efficiency. Our dream is to use this model to make a genetic map of human germ-cell differentiation, including some of the very earliest stages.”

Unlike many other cellular and physiological processes, human reproduction varies in significant ways from that of common laboratory animals like mice or fruit flies. Furthermore, many key steps, like the development and migration of primordial germ cells to the gonads, happen within days or weeks of conception. These challenges have made the process difficult to study.

Reijo Pera, who is now a professor of cell biology and neurosciences at Montana State, is the senior author of a paper describing the research, which was published May 1 in Cell Reports. The experiments in the study were conducted at Stanford, and Stanford postdoctoral scholar Cyril Ramathal, PhD, is the lead author.

Infusion of young blood recharges brains of old mice, researchers find

By Bruce Goldman

Something — or some things — in the blood of young mice has the ability to restore mental capabilities in old mice, a new study by School of Medicine investigators has found.

If the same goes for humans, it could mean a new paradigm for recharging our aging brains, and it might mean new therapeutic approaches for treating dementias such as Alzheimer’s.

In the study, published online May 4 in Nature Medicine, the researchers used sophisticated techniques to pin down numerous important molecular, neuroanatomical and neurophysiological changes in the brains of old mice that shared the blood of young mice.

But they also conducted a critical experiment that was far from sophisticated, said Tony Wyss-Coray, PhD, the senior author of the study and a professor of neurology and neuroscientific sciences. The scientists simply compared older mice’s performance on standard laboratory tests of spatial memory after these mice had received infusions of plasma (the cell-free part of blood) from young versus old mice, or no plasma at all.

“This could have been done 20 years ago,” said Wyss-Coray, who is also senior research career scientist at the Veterans Affairs Palo Alto Health Care System. “You don’t need to know anything about how the brain works. You just give an old mouse young blood and see if the animal is smarter than before. It’s just that nobody did it.”

Wyss-Coray has co-founded a biotechnological company.

See blood, page 5

Center aims to strengthen quality of scientific research

By Kris Newby

A new center at Stanford aims to transform research practices to improve the reproducibility, efficiency and quality of scientific investigations.

Scholars at the Meta-Research Innovation Center, or METRICS, will focus on conducting research about research. Their mission: to promote excellence in research through collaborations around the world. The center’s launch has been made possible through a $6 million grant from the Laura and John Arnold Foundation.

The center will be co-directed by John Ioannidis, MD, DSc, professor of medicine and of health research and policy and director of the Stanford Prevention Research Center, and Steven Goodman, MD, MHS, PhD, professor of medicine and of health research and policy and associate dean for clinical and translational research at the School of Medicine.

“Scientists have made amazing discoveries to date, but we have an opportunity to accelerate advances,” said Steven Goodman (left) and John Ioannidis will direct a new Stanford center focused on identifying weaknesses in the way scientific research is conducted and offering methods for improvement.

Ioannidis has devoted much of his career to empirically testing and evaluating ways to enhance the efficiency. We will be looking for ways to reduce biases in study design, data interpretation and outcomes reporting.”

The problems with research

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See METRICS, page 8

At a time when reproducibility, mean-
Health-care aid boosts life expectancy in developing countries

By Ruthann Richter

Todd Park, chief technology officer of the United States, will be among the featured speakers at the Big Data in Biomedicine conference May 21-23 at the Stanford University School of Medicine.

The conference, jointly sponsored by Stanford Medicine and Oxford University, will highlight opportunities for mining the rich repositories of biomedical information available today. The gathering will bring together hundreds of participants from academia, information technology corporations, venture capital firms, the U.S. government and foundations interested in harnessing the potential of big data to improve human health around the globe. The event will be held at the Li Ka Shing Center for Learning and Knowledge on the Stanford campus.

"We are excited to bring together such a diverse group of participants," said Euan Ashley, MD, PhD, associate professor of medicine and of genetics and director of the Stanford Clinical and Translational Science Institute. "This conference will be an important step toward unlocking the potential of large-scale data for biomedical research.

"Our ability to extract new knowledge from large-scale databases will transform the way we think about disease," said Ashley. "Together, we can lead to new methods of prevention and treatment." Minior said. "The conference will help bring us closer to this goal by providing a hub to discuss big data, page 3
Big data
continued from page 2

a forum for knowledge-sharing in the field. We are very grateful to the Li Ka Shing Foundation. All sponsors who took the time to support this effort."

Several leading Stanford scientists will participate in the conference, including Sylvia Eplevitis, PhD, professor of radiology; Julie Parsonnet, MD, professor of medicine and director of the Stanford Prevention Research Center; Stephen Quake, MD, PhD, professor of bioengineering; Michael Snyder, MD, PhD, professor and chair of genetics. In addition, Paul Yock, MD, PhD, professor of medicine and bioengineering; Greg Kovacs, MD, PhD, professor of electrical engineering; Michael Mc- the baby was taken out, because delivery relieves com- pressure of the uterus on the major veins. That's the first step. Histori- cally, some experts suggested tilting the patient's entire body to the left, but it's extremely difficult to give effective compressions on a tilted system.

Step two is that the team should deliver the baby as part of resuscitation for the mom. Historically, teams tried to save the mom for 45 minutes or an hour and then, if they couldn't revive her, they would try to get the baby out. But there have been case reports in which women spontaneously got their circulation back after the baby was born, because delivery relieves com- pression on mom's circulatory system. Delivery im- proves maternal survival as well as fetal neurological outcome and may improve maternal mortality. This was a huge shock to everyone. It turned out that before non-emergency ce- sareans, the obstetric technicians add a scalpel at the last minute because of the handle of our scalpel is plastic and would melt in the autoclave. Now we keep a separate, sterilized scalpel in a locked drawer in every la- bor room. Simulations also help the staff learn their roles so that each person knows what to do in a real emergency. 11

For first time, school to offer 12 full-tuition scholarships
By Tracie White

Beginning with the 2014 entering class, the School of Medicine will offer 12 full-tuition scholarships to students whose family income falls below three times the federal poverty level. "At Stanford Medicine, we are training the future leaders of the biomedical revolution, and that means ensuring that cost does not deter the best and brightest students," said Lloyd Minor, MD, dean of the medical school. "These new full-tuition scholar- ships demonstrate our strong commit- ment to excellence and diversity."

With the cost of tuition now run- ning about $56,000 per year, each of these need-based scholarships will be worth about $200,000 per student over four years. They are the first full-tuition scholarships offered by the school.

In addition, the maximum grant for the standard need-based program will be raised this year to $5,500 per quarter, a 4.5 percent increase, and institutional financial aid resources will be extended to international students.

Financial aid currently includes need- based grants, a matching grant program for middle-income students, and the ability for students to incorporate work- study (teaching assistantships) to offset living expenses. The average entering class has 90 students.

"We've never had a time where we've covered the entire cost of tuition," Prober said. "The maximum grant does not cover full tuition."

"For students, many medical students graduate with an average debt of about $100,000, Prober said, which is low when com- pared to the school's peer institutions. "In addition to the financial aid pro- gram, he attributes this low graduating debt to the fund- ing that is provided to stu- dents through the medical school program in support of scholarly work, teaching assistantships that are pur- sued by most of the students, and student success in ob- taining competitive academic scholarships from outside sources, such as the Howard Hughes Medical Institute."

"We believe we've done quite well historically," Prober said. "But we need to graduate with among the lowest debt."

Still, that debt remains substantial, and his goal is to make the fewest resources the hardest, he said.

"We want to make a Stanford medical education an option for all persons who qualify for admission to our school," Prober said, noting the school has a need-blind admissions policy.

The metric used to determine who is eligible for the new scholarships is based on the federal pov- erty guidelines set each year by the U.S. Depart- ment of Health & Hu- man Services. Students whose family income falls below three times the poverty level, based on the federal guidelines, and have total financial assets of $250,000 or less are eligible. 11

3

Stanford, with its excellence in computer science, engineering, statistics, genetics and bioinformatics, as well as its connec- tions to Stanford's Center for Innovation and data management and analysis.

"We believe that we will build bridges between the world's large databanks of health information and develop new and innovative methods of analyzing information, among other projects, Ashley said.

The cost of the conference ranges from $300 for a single day to $750 for the full three days. For more information or to register, go to http://bigdata.stan- ford.edu. 11

Brendan Carvalho on CPR for pregnant patients

When a pregnant woman's heart stops, two lives are threatened. But until now, car- not adequately emphasize key differences in the CPR technique for pregnant patients nor given operational strategies to improve survival of both the expectant mom and her fetus. Stanford anesthesiologists Brendan Carvalho, MD, Steven Lipman, MD, and Sheila Cohen, MD, led a team of experts assembled by the Society for Obstetric Anesthesia and Perinatology that has produced new expert recommendations, published in the May issue of Anesthesia & Analgesia, describing how to treat cardiac arrest in pregnant women. Carvalho, who is chief of obstetric anesthesia at Lucile Packard Children's Hospital Stan- ford and associate professor of anesthesiology, perioperative and pain medicine, talked with science writer Erin Digita about the new recommendations and why they're needed.

1 Why was the consensus statement needed, given that cardiac arrest in pregnancy is now rare? We've cut maternal mortality significantly over the past century, but maternal death can still happen to any pregnant woman. Treatment women need to know how to handle cardiac arrest. The American Heart Association publishes guideline statements on CPR, but special populations such as pregnant women are not adequately highlighted. The Society for Obstetric Anesthesia and Perinatology recently revised its guidelines and issued a con- sensus statement by a team of experts. Stanford faculty led this effort and contributed a number of members to the expert team, including Daniel Ganster, Julie Parsonnet, and Mauricio Druzin. We came up with expert recommend- ations that clearly identify pregnancy CPR as a neglected aspect of resuscitation care. With better management of cardiac arrest in pregnancy, we can improve outcomes.

2 Why are women at risk for cardiac arrest in preg- nancy and why? Cardiac arrest affects less than one in 20,000 preg- nant women, occurring most frequently during labor and delivery. Women with high-risk pregnancies are at increased risk, such as those with cardiac disease. We're seeing this situation more frequently as sicker and older women are having babies. But some causes of cardiac arrest, such as hemorrhage, can affect any healthy, preg- nant woman. Anoxic fluid or pulmonary embolus, in which the blood from the heart stops. Thus, if the blood stream and triggers a cardiac collapse, can also affect any pregnant woman. When cardiac arrest actually occurs, which is what our consensus statement addresses, you need to know how to optimize care. If you don't do the best possible care and not withhold any drugs or procedures that would normally be used managing a critically ill person.

3 How should resuscitation be modified for a pregnant patient? When a patient's uterus becomes enlarged, it puts pressure on the big blood vessels that return blood to the heart. This can make it difficult to perform emergency CPR. In a nonpregnant patient, we can usually generate about 20 to 30 percent of normal cardiac output with CPR. But most compressions generate only 10 to 15 percent of normal cardiac output. To maximize survival, we recommend left uterine displacement: In addition to the person doing chest compressions, resuscitation team members should have a separate person who pushes the uterus to the patient's left side to relieve pressure of the uterus on the big veins. That's the first step. Histori- cally, some experts suggested tilting the patient's entire body to the left, but it's extremely difficult to give effective compressions on a tilted system.

Step two is that the team should deliver the baby as part of resuscitation for the mom. Historically, teams tried to save the mom for 45 minutes or an hour and then, if they couldn't revive her, they would try to get the baby out. But there have been case reports in which women spontaneously got their circulation back after the baby was born, because delivery relieves compress- ion on mom's circulatory system. Delivery im- proves maternal survival as well as fetal neurological outcome and may improve maternal mortality. Step two is that the team should deliver the baby as part of resuscitation for the mom. Historically, teams tried to save the mom for 45 minutes or an hour and then, if they couldn't revive her, they would try to get the baby out. But there have been case reports in which women spontaneously got their circulation back after the baby was born, because delivery relieves compress- ion on mom's circulatory system. Delivery im- proves maternal survival as well as fetal neurological outcome and may improve maternal mortality.

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3
New tool improves ability to use light for switching off cells

By Tom Abate

In 2005, a Stanford scientist discovered how to switch brain cells on or off with light pulses by using special proteins from microbes to pass electrical current across cell membranes.

Since then, research teams around the world have used this technique that this scientist, Karl Deisseroth, MD, PhD, dubbed “optogenetics” to study not just brain cells but heart cells, stem cells and the vast array of cell types across biology that can be regulated by electrical signals — the movement of ions across cell membranes.

Optogenetics gave researchers a powerful investigational technique to deepen their understanding of biological system design and function in animal models. But first-generation optogenetics had a shortcoming: Its light-sensitive proteins were potent at switching cells on, but less effective at turning them off.

In a paper cementing years of effort, Deisseroth’s team has re-engineered their light-sensitive proteins to switch cells off far more efficiently than before. The paper was published April 25 in Science.

“This is something we and others in the field have sought for a very long time,” said Deisseroth, senior author of the paper and professor of bioengineering and of psychiatry and behavioral sciences.

Thomas Insel, MD, director of the National Institute of Mental Health, which funded the study, said this improved “off” switch will help researchers to better understand the brain circuits involved in behavior, thinking and emotion.

“This latest discovery by the Deisseroth team is the kind of neurotechnological advance that President Obama when he launched the BRAIN Initiative a year ago,” Insel said. “It creates a powerful tool that allows the kind of neurotechnology envisioned by President Obama to continue flowing, even after the light was turned off.

“This discovery pointed to a potential strategy to create an inhibitory channel: bioengineer the opsin to create an inner lining of positive amino acids to draw a flow of negative (inhibitory) ions, such as chloride, into the cell.”

From that point, it took roughly another two years for Deisseroth’s team, led by Andre Berndt, PhD, and Soo Yeun Lee, PhD, postdoctoral scholars in bioengineering and lead authors of the paper — to complete this process.

In order to create this new lining, the Stanford team re-engineered the excitatory channel opsin from their 2012 experiment to change nine of the protein’s roughly 300 amino acids.

When triggered by light, this newly bioengineered protein now opened a channel lined by more positively charged amino acids and thereby attracted a flow of negative (chloride) ions to inhibit activity. This created a microbial opsin capable of delivering a powerful channel effect for inhibition.

“Looking ahead

As the Stanford team continues a 10-year journey that began with its first microbial opsin experiments in neurons, Deisseroth anticipates that the long-acting and stable responses of SwiChR will open new realms of opportunities for optogenetics.

His enthusiasm was echoed by Merab Kokaia, PhD, a professor at Lund University Hospital in Sweden who has used optogenetics to study epilepsy, among other conditions, in rodent models. Kokaia, who was not involved in the Deisseroth team’s new study, noted the new opsin’s main advantages: more effective at inhibiting neuronal activity based on chloride conductance, greater sensitivity to light, and the ability to stay open for longer periods and maintain inhibition even without light for longer periods.

“These features could be much more useful for behavioral studies in mice to develop an effective treatment alternative for neurological conditions where drugs do not work, such as some cases of severe epilepsy and other brain disorders,” Kokaia said.

“The novel approach of channel engineering used by Deisseroth’s lab opens unprecedented perspectives for developing new optogenetic tools for system neuroscience studies that will help us to understand better how the brain works.”

Chuch Ramakrishnan, a research assistant in the Deisseroth lab, also was a co-author of the study.

The research was supported by the National Institute of Mental Health, the Simons Foundation, the National Institutes of Health’s National Institute on Drug Abuse, the National Institutes of Health’s National Center for Advancement Research Projects Agency, the Gatsby Foundation and the Wiegert Family Fund.

The development of Bioengineering also supported the work.

Tom Abate is the director of communications at Stanford Engineering.

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whose circulatory systems had been reversed. They're not final,” Villeda said. In an effort to explore his interest in pediatrics, Gregory Gaskin, another second-year medical student, has been working with Arash Anoshiravani, MD, assistant clinical professor of pediatrics, in Santa Clara County juvenile detention facilities. His poster presentation was titled “Mortality among former juvenile offenders in California.”

By Tracie White

The research interests of Stanford medical student Alkahut, to explore the therapeutic implications of the new study’s findings, he serves as a faculty fellow at UC–San Francisco. Villeda was a graduate student at Stanford and, briefly, a postdoctoral scholar under Wyss-Coray’s direction when the work was performed.

“We've shown that at least some age-related impairments in brain function are reversible. They’re not final,” Villeda said. Previous experiments by Wyss-Coray, Villeda and her colleagues, described in a paper published in 2011 in *Nature Medicine*, has been working with Arash Anoshiravani, MD, clinical assistant professor of pediatrics, and, like many of the students participating in the symposium at the Li Ka Shing Center for Learning and Knowledge, Laidlaw chose a field of research that she has considered pursuing after graduation.

In both tests, the improvement vanished when the old mice had first been subjected to high temperatures. Heat treatment can denature proteins, so this hints that a blood-borne protein, or group of them, may be responsible for the cognitive improvements seen in old mice given young mouse plasma.

“Those are factors present in blood from young mice that can recharge an old mouse’s brain so that it functions more like a younger one,” Wyss-Coray said. “We're working intensively to find out what those factors might be and from exactly which tissues they originate.”

“We don’t know yet if this will work in humans,” he said, adding that he hopes to find out sooner rather than later. A near-term goal of his company is to test this proposition through a clinical trial. Another Stanford co-authors were Frank Greenfield, MD, PhD, and Joseph Castellano, PhD; graduate students including Arash Anoshiravani, MD, and Michael Longaker, MD, professor of surgery.

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Scientists identify source of most cases of invasive bladder cancer

By Krista Conger

A single type of cell in the lining of the bladder is responsible for most cases of invasive bladder cancer, according to researchers at the School of Medicine. The research, conducted in mice, is the first to pin down the normal cell type that can give rise to invasive bladder cancers. It’s also the first to show that most bladder cancers and their associated precancerous lesions arise from just one cell, and explains why many human bladder cancers recur after therapy.

“Although the cancer stem cells, and the precancerous lesions they form in the bladder lining, express an important signaling protein called sonic hedgehog, the cells of subsequent invasive cancers invariably do not — a critical switch that appears vital for invasion and metastasis. This switch may explain certain confus- ing aspects of previous studies on the cellular origins of bladder cancer in humans. It also pinpoints a possible weak link in cancer progression that could be targeted by therapies.”

Choosing a model

Many animal models of cancer rely on prior knowledge or hunches as to what genes or cell types are involved. Researchers may genetically alter an animal, or a group of cells, and observe what happens. It is expensive and difficult to determine how human tumors arise, because even the most advanced, invasive carcinomas in humans could make sense in this context because cancer is essentially a loss of normal regulation.”

“After four months of BBN treatment,” Beachy said, “we’d often see one color dominating the entire epithe- lium. This clearly indicates that a single cell has taken over the lining of the entire bladder, elbowing out its neighbors in a way that’s not been seen in other organs.”

Further studies showed that, surprisingly, none of the cells in the most advanced, invasive carcinomas in the BNN-treated animals expressed sonic hedgehog, despite the fact that only sonic-hedgehog-expressing cells are able to give rise to the earliest stages of blad- der cancer. One obvious implication of the lack of sonic hedgehog expression in these cells is that the hedgehog pathway somehow inhibits stem cell development. More fundamentally, it suggests that the sonic-hedgehog pathway somehow inhibits stem cell development. More fundamentally, it suggests that the sonic-hedgehog pathway might be a critical target for cancer therapies.”

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Kris Newby is the communications man-ager for Stanford Medicine.

METRICS continued from page 1

ing that an experiment can be reproduced with the same results, is key to validating and building on scientific findings. Ioannidis is one of the highly cited scientists in his generation in the scientific literature, according to Micro- soft Academic Rankings. He is best known for his 2005 PLoS Medicine paper “Why most published research findings are false,” which is the most accessed and downloaded article in the history of Pub- lic Library of Science, with more than 1 million views.

Goodman’s research is focused on sci- entific inference, the process of using sta- tistical analysis to develop scientific beliefs in the presence of uncertainty. He has spent much of his career trying to improve the accuracy of scientific inference and understanding research. He is the senior statistical editor of the Annals of Internal Medicine, vice-chair of the methodology committee of the federal Patient-Centered Outcomes Research Institute and, for the past decade, editor-in-chief of the journal Clin- ical Trials.

“All scientists share the common goals of searching for truth and of improving their methods,” said Goodman. “But it is often a difficult task to know which research and reporting practices actually lead to the greatest conclusions. Without scientifi- cal inference research, the domain of the meta-research.”

Recent public concern about research credibility has prompted the government to take action. On Jan. 27, Francis Col- lin, the NIH director and head of the National Institutes of Health, announced a series of initiatives to enhance NIH-supported research.

METRICS plans to work closely with researchers and policymakers on this is- sue. As a first step, the center named Denver-based researchers to an NIH National Cancer Institute (NCI) Institutional Review Board (IRB) to provide guidance on the latest policy and methods discussed in the journal Clinical Trials. In this role as the center’s coordinating team, the center’s public health and research staff field questions from the community, including researchers, about how to design and analyze clinical research.
Skin cells

author of the paper.

reproductive medicine and surgery program. While the study clearly demonstrates the importance of genet-

ic function in sperm biology, it also suggests that some of these limitations could potentially be overcome," Eisen-

erberg often collaborates with Reijo Pera, but he was not

of the nervous system. In 2009, Reijo Pera showed that it is possible to generate functional, sperm-producing germ cells from skin cells grown in certain con-

ditions in the laboratory. However, these stem cells, which were made from human embryos that had been

for research in vitro fertilization procedures, can be difficult to come by. They also are not useful for couples wishing to have their own genetic children because the child would inherit a portion of the father's genome from which the cells were derived. Furthermore, the process required scientists to engineer the stem cells so they would overexpress several proteins which drive the embryonic stem cells to become germ cells.

In contrast, the stem cells made from adult skin re-
sults, he used a technique that had allowed him to

ing to peer into the brains of mice to watch in real time to see if the drug was

properly, as in Alzheimer's or Parkinson's diseases, or other disorders of the brain. The proteins could also be inserted in neurons in a lab dish. Scientists de-

veloping drugs, for example, could expose human nerves in a dish to a drug and watch in real time to see if the drug changes the way the nerves fire. If those neurons in the dish represent a disease, like Parkinson's, a scientist could look for drugs that cause those cells to fire more normally.

For more than a decade, neurosci-

ents and other proteins like voltage sensors, the two teams

voltage sensors, the two teams

also got joint funding through a Bio-X Ventures grant, now associated with the Stanford Neurosciences Institute, to develop new ways of imaging neural activity deep in the brain. That work will add one more tool for understanding how the complex neural circuits that connect us make us who we are.

Other Stanford co-authors of the Schnitzer team’s paper were Mark Wagner, a graduate student, and Jin Zhong Li, PhD, director of molecular vi-

ology. Other Stanford co-authors of the Lin team’s paper were graduate student Jesse Marshall and postdoctoral scholar Yixin Wu.

Schnitzer’s study was funded by the Defense Advanced Research Projects Agency, the Stanford Cracking the Neu-

tural Code Program, Stanford Bio-X, the National Institutes of Health-Stanford Neurosciences Graduate Training Grant and the National Academies Keck Fu-

ture Initiative.

Lin’s study was funded by the Na-

tional Science Foundation, a Walter V. and Idun Berry Postdoctoral Fellowship, Stanford Bio-X, the Stanford Cracking the Neural Code Program and the Na-

tional Academy of Sciences Keck Futures Initiative.

Amy Adams is director of interdisciplinary life sciences communications in the Office of University Communications.

Medical school senate meeting scheduled for May 20

The next meeting of the medical school’s faculty senate is scheduled from 5:15 to 6:30 p.m. May 20.

Pree Bassavaj, clinical associate professor of medicine and chair of the Curriculum and Academic Policy Committee, will present a report from the faculty senate.

Neil Gesundheit, MD, MPH, professor of medicine and associate dean for medical education and chair of the Committee on Curriculum Development, will discuss the latest plans for the teaching and curriculum development.

Nancy Gump, PhD, professor of obstetrics and gynecology and chair of the Committee on Performance, Policy and Administration, will present a report to the committee.

Interim reports from the Subcommittee on the General Welfare of the faculty and the Senate Committee on Research and the Subcommittee on Education were also presented.

Medical school faculty can download the complete minutes of senate meet-

ings by visiting http://med.stanford.edu/senate.
Brain mapping gives hope to people with intractable epilepsy

By Sara Wykes

For nine years, Laura Koellstedt tried as hard as she could to lead a normal life. It was not easy. Every day, from deep within her brain, a cluster of cells would fire all at once, out of sequence, as out of control as a fast-moving storm.

Those cellular misfires Koellstedt experienced were seizures. Hers were so frequent, unpredictable and debilitating — her right leg would kick out uncontrollably and she would fall to the floor — that she wasn’t safe doing anything. She couldn’t care for her two young children. She couldn’t work. She couldn’t drive. Finally, in desperation, she moved into bed, and when she had to move around her home, she crawled instead of walking.

Sometimes medications would work, but not permanently. Rain Parvizi, a Stanford neurologist who’s become one of those physicians whose seizures become intractable to medication — and she turned to Stanford’s Intractable Epilepsy Program for help. Epilepsy specialists from several medical and scientific disciplines were part of the team that used advanced forms of seizure mapping (to pinpoint the source of Koellstedt’s seizures) and functional brain mapping, safely enabling the surgery that returned the 38-year-old resident of Albany, Calif., to a normal life.

“Treating intractable epilepsy is like a hunt with many stones and turns,” said Josef Parvizi, MD, PhD, associate professor of neurology and neurological sciences and director of the Intractable Epilepsy Program. “Each patient’s seizures are unique, with a specific pattern and a unique seizure network that the abnormal brain waves traverse.”

Once, neurologists did not have a technology to determine the brain of epileptic seizures deep within the brain. Now, with state-of-the-art technology, they can apply the highest power of magnetic-resonance imaging — scans of the brain — to look for the area of seizure causes, including scars and lesions. They can also use a video-electroencephalography to gauge electrical activity in the brain.

But when a seizure’s source is deep in the brain, as Koellstedt’s was, physicians must place electrodes directly into the brain, the skull interface with seizure detection. Doctors will either place a set of electrodes in a gridlike netting on the brain or place individual electrodes into strategically selected areas, “like a puzzle,” Parvizi said. The detailed method of seizure hunting involves a combination of this intracranial recording and functional brain mapping, where doctors stimulate the seizure area through the electrodes to determine what body function is controlled by that area.

“Implicating electrodes over the surface of the brain allows us to go beyond the skull,” Parvizi said, “so we can listen to what’s happening from inside the brain instead of what we can hear from the outside. From the outside you can only detect the explosions of electrical activity, but you can’t hear who is who in epilepsy and who is saying what to whom.” Using this functional brain-mapping technique provides important information crucial for identifying the source of Koellstedt’s seizures.

The Stanford team worked with a researcher at the institute to develop a new antibody-drug conjugate that would act as a treatment against breast cancer. They turned to Ruth O’Hara, an associate professor of surgery, effective Oct. 1.

“Her research focuses on genome sequence and function in both humans and related primates, mammalian and vertebrate species. He is interested in mapping both coding and noncoding genome sequence variations at both genome and transcriptome differences, and in extracting specific genetic insights from high-throughput sequencing measurements, in the contexts of development and developmental abnormalities,” Koellstedt said.

Mark Buyukyounouski, MD, was appointed associate professor of radiation oncology, effective Oct. 1.

Koellstedt said her first moment in the recovery room was “I was in agony. Even without feeling, I could learn to function again as a human being.” The anesthesia team came in and made treatment an even more delicate task than usual. Her seizures came from the part of the brain that controls sensation and movement in her legs, an area difficult to see or listen to because it’s where the two halves of the brain overlap. “With thick bone and such a deep source, we would have been blind to the seizure’s origin if not a neural brain waves by just listening through the skull,” Parvizi said.

With the electrodes placed near the origin of Koellstedt’s seizures, Parvizi said, “it would make it difficult to determine what body function was controlled by that part of her brain. After a fourth day of testing and mapping her brain in the hospital, Parvizi came to Koellstedt’s room and said, ‘We found it. We’re going to get it.’

Before the team proceeded, they warned Koellstedt of the risk: If something went wrong with the surgery, if the wrong area was removed, she might lose feeling in her legs. “I didn’t care,” Koellstedt said. “I was in agony. Even without feeling, I could learn to function again as a human being. I could be a mother to my children and a wife to my husband. And I could go back to work.”

The surgery took eight hours. The degree of precisioin the brain, which the neurosurgeon did not use a scalpel. Instead, she suctioned out cells, removing just those in the main hub of the seizure source. Koellstedt recalled her first moment in the recovery room, “I remember waking up and someone saying, ‘Can you move your foot? I said, ‘Yes,’ and they said, ‘OK, you’re not paralyzed.’ I remember being very happy and going back to sleep.”

“With patients with intractable epilepsy come to Stanford for treatment,” Parvizi said, “what they will find is a unique team that fuses clinical care and science. We collaborate with our colleagues in multiple departments throughout Stanford Hospital & Clinics and Stanford University, including computer science, engineering, psychology and radiology. We get together to improve our current methods or to invent entirely new ways of mapping the brain, which will at the end lead to better treatment options for our patients. On the clinical side, we also get together to discuss each and every single epilepsy surgery case. We meet on a weekly basis, and a group of 10 to 20 clinicians who aren’t afraid of opposing each other brainstorm about the best treatment options for individual patients.”

Koellstedt still takes a couple of medications to control her seizures, which have now stopped completely. She helped her convince the California Department of Motor Vehicles to let her take a driver’s test to regain her license. She passed.

Sara Wykes is a writer in the communications office at Stanford Hospital & Clinics.

OF NOTE

GILL BEJERANO, PhD, was promoted to associate professor of developmental biology, effective March 1. His research focuses on genome sequence and function in both humans and related primates, mammalian and vertebrate species. He is interested in mapping both coding and noncoding genome sequence variations at both genome and transcriptome differences, and in extracting specific genetic insights from high-throughput sequencing measurements, in the contexts of development and developmental abnormalities.

MARK BUYUKYOUNOUSKI, MD, was appointed associate professor of radiation oncology, effective Oct. 1.

KAY YAM CHAK, PhD, a postdoctoral scholar in neurology and neurological sciences at Stanford, who recently won fourth place in the Breast Cancer Startup Competition, held by the Avon Foundation for Women in conjunction with the National Cancer Institute and the Center for Advancing Innovation, challenged 200 teams to develop a breakthrough technology that would have the potential to advance breast cancer research. The Stanford team worked with a researcher at the institute to develop a new antibody-drug conjugate that would act as a treatment against breast cancer.

AMY GALLO, MD, was appointed assistant professor of surgery, effective Oct. 1.

BONNIE HALPERN-FELSHER, MD, was appointed associate professor of radiology, effective March 1. She is interested in cognitive and psychosocial factors involved in adolescents’ and young adults’ health-related decision-making, perceptions of risk and vulnerability, health communication, and risk behavior in adolescents and young adults.

RUTH O’HARA, PhD, was appointed associate professor of psychiatry and behavioral sciences, with tenure, effective April 1. (She previously held a nontenure-line position.) Her research aims to identify physiological markers of neurocognitive impairment in a broad range of psychiatric disorders, including autism spectrum disorders, mild cognitive impairment and late-life depression and anxiety.

MANU PRAKASH, PhD, assistant professor of bioengineering and graduate student GEORGE KORIRI recently won a contest to develop the 21st-century cancer treatment set. The Baby & Young Adult Cancer Search Kit Competition was jointly sponsored by the Gordon and Betty Moore Foundation and the Society for Science & the Public. The team won a $50,000 award toward further developing the 55-minute cancer treatment kit. The team consists of bioengineers, computer scientists and addressing developing-world problems, such as water quality.

STEPHEN QUAKE, PhD, the Lee Otterton Professor in the School of Engineering, professor of bioengineering and Howard Hughes Medical Institute investigator, is one of 11 Stanford professors recently elected as members of the American Academy of Arts and Sciences. The academy is one of the country’s oldest and most prestigious honoraries learned and a leading center for independent policy research.

DEBRA SAFFER, MD, was promoted to associate professor of psychiatry and behavioral sciences, effective March 1. Her primary research interests include the nature and treatment of eating disorders (particularly bulimia nervosa and binge-eating disorder), the development and treatment of obesity, and the development and treatment of problematic eating patterns in patients following bariatric surgery.

DAVID SPEIGEL, MD, the Jack, Samuel and Lulu Willson Professor and professor and associate chair of psychiatry and behavioral sciences, is the recipient of the 2014 Joan and Stanford Alexander Award in Psychiatry. The award was established in honor of Stuart Yudofsky, MD, professor and chair of the Menninger Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine, who was also his first recipient. Speigel, who was chosen for his research on stress and health, accepted the award April 30 and presented a lecture titled "Mind Matters: Stress, Support and Cancer Survival."