New chapter for Stanford Hospital

By Ruth Schechter

For Chis Bowers, the construction workers, dump trucks and diggers around Stanford Hospital & Clinics are a vivid reminder of what the hospital renewal project is all about: caring for patients.

Diagnosed in 2009 with cancer, Bowers was one of the speakers at the groundbreaking ceremony May 1 for the new hospital. He credits Stanford with saving his life. “It is my privilege and honor to speak for the patients this afternoon,” said Bowers, a resident of Los Altos Hills. “I was diagnosed, treated at Stanford, and I survived. I am thankful to the people at Stanford who healed me and am happy to be part of what this event will mean to future patients.”

About 400 administrators, donors and community members gathered under an enormous white tent to watch as shiny red shovels were put to ceremonial dirt, marking the formal start of construction and a new chapter in the history of Stanford Hospital & Clinics.

Attendees looked out through a clear-paneled wall of the tent onto the excavation site, where immense yellow trucks and diggers stood motionless for the evening.

“Our vision here at Stanford Hospital & Clinics is to heal humanity, through science and compassion, one patient at a time,” said Amir Dan Rubin, the hospital’s president and CEO. “The hospital is embedded in the university, collaborating with engineering, computer science, law, and it’s embedded in Silicon Valley. These collaborations are part of what I call the ‘Stanford edge,’ and part of our commitment to heal with comfort, compassion and service.”

Scheduled to open to patients this afternoon, the speakers at the groundbreaking ceremony May 1 may have imagined,” said Barna. “These extremely fine, very long extensions can reach several cell diameters away. We have visualized these fascinating structures in mesenchymal cells but they may be a more generalized feature of many additional cell types.”

Barna and her colleagues found that signaling molecules are released from one cell and float, or diffuse, through the intercellular space to their targets. While this finding does not preclude the use of diffusion as a signaling method, it identifies another new, surprising avenue of long-distance cell-cell communication.

By Krista Conger

Discovery alters scientists’ understanding of long-distance intercellular communication

By Erin Digitale

Why do some children learn math more easily than others? Research from the School of Medicine has yielded an unexpected new answer.

In a study of third-graders’ responses to math tutoring, Stanford scientists found that the size and wiring of specific brain structures predicted how much an individual child would benefit from math tutoring. However, traditional intelligence measures, such as children’s IQ’s and their scores on tests of mathematical ability, did not predict improvement from tutoring.

The research is the first to use brain scans to look for a link between math-learning abilities and brain structure or function, and also the first to compare learning abilities and brain structure or function, and also the first to compare learning abilities and brain structure or function.

Researchers understand the origins of math-learning disabilities.

Study: Kids’ brain features predict degree of benefit from math tutoring

By Krista Conger

In a finding likely to fundamentally reshape biologists’ understanding of how vertebrate cells communicate, researchers at the School of Medicine and UCSF have discovered a new type of cellular structure that directly delivers and receives payloads of signaling molecules between distant neighbors in a developing embryo.

The seeming specificity of the interaction contrasts starkly with the commonly held notion that signaling molecules are released from one cell and float, or diffuse, through the intercellular space to their targets. While this finding does not preclude the use of diffusion as a signaling method, it identifies another new, surprising avenue of long-distance cellular communication.

The research was published online April 28 in Nature.

“When the presence of these structures, which we call cytoplasmic extensions or a type of specialized filopodia, was really unexpected,” said Maria Barna, PhD, an assistant professor of developmental biology and of genetics at Stanford. She and her colleagues used high-resolution, real-time imaging techniques to see the previously invisible extensions that form finger-like projections. These projections are destroyed by conventional techniques that are used to preserve tissues.

“We now know that the morphology of a typical cell in a vertebrate embryo looks very different than what we would have imagined,” said Barna. “These extremely fine, very long extensions can reach several cell diameters away. We have visualized these fascinating structures in mesenchymal cells but they may be a more generalized feature of many additional cell types.”

(Barna, a former UCSF faculty fellow, is the senior author of the research. Postdoc toral scholars Esther Llagostera, PhD, of Stanford, and Timothy Sanders, MD, PhD, of UCSF, are lead authors of the paper.

“This work suggests that the cells within the embryonic limb tissue are interconnected by a dense network of dynamic extensions that mediate communication across a broad terrain,” said Deborah Yelon, professor and vice chair of cell and developmental biology at UC-San Diego. “This ‘network’ view of long-distance signaling is a striking contrast to previous ‘signal diffusion’ or ‘bucket brigade’ models and has the potential to revamp the textbook view of the mechanisms of tissue patterning.”

Yelon was not involved with the study.

Barna and her colleagues found that the newly identified, nearly invisible finger-like projections reach out across relatively long distances to touch those of other cells.

“These mesenchymal cells have developed long, finger-like projections that reach out across relatively long distances to touch those of other cells.
Study examines cost-effectiveness of helicopter transport

By Sara Wykes and John Sanford

Researchers at the School of Medicine have for the first time determined how often emergency medical helicopters need to save the lives of seriously injured people to be considered cost-effective compared with ground ambulances.

The researchers found that if an additional 1.6 percent of seriously injured patients survive after being transported by helicopter from the scene of injury to a level-1 or level-2 trauma center, then such transport should be considered cost-effective. In other words, if 90 percent of seriously injured trauma victims survive with the help of ground transport, 91.6 percent need to survive with the help of helicopter transport for it to be considered cost-effective.

The study, published online in April in the Annals of Emergency Medicine, does not address whether most helicopter transport actually meets the additional 1.6 percent survivorship threshold.

“What we aimed to do is reduce the uncertainty about the factors that drive the cost-effective use of this important critical-care service,” said the study’s lead author, M. Kit Delgado, MD, MS, an instructor in the Division of Emergency Medicine.

“The goal is to continue to save the lives of those who need air transport, but spare flight personnel the additional risks of flying to very low-density populations and save the added cost when helicopter transport is not likely to be cost-effective,” Delgado added. (Helicopter medical services generally bill patients’ insurance providers directly, but patients may have to pay some of the bill out of pocket, or, if they’re uninsured, possibly all of it.)

The study comes at a time when finding ways to cut medical costs has become a national priority, because the overuse of helicopter transport has come under scrutiny. Previous studies have shown that, on average, over half of patients transported by helicopter have only minor, non-life-threatening injuries. For these patients, transport by helicopter instead of ground ambulance is not likely to make a difference in outcomes, and the additional risk and cost of helicopter transport outweighs the benefit, Delgado and other authors write.

In 2010, there were an estimated 44,700 U.S. helicopter transports from injury scenes to level-1 and level-2 trauma centers, with an estimated average cost of about $6,500 per transport. (Level-1 and -2 trauma centers are hospitals equipped and staffed to provide the highest levels of surgical care to trauma patients; level-1 centers offer a broader array of medical services than level-2 centers and also are committed to research and teaching efforts.)

Yet emergency helicopter transport sits in a cost-efficiency conundrum: It is most needed in remote, rural areas where transport by ground can take far longer. In these areas, there are also risks to have sparser populations and therefore fewer calls for aid, making it difficult to recoup the overhead costs of maintaining helicopter services, Delgado said.

In some areas of the country, however, helicopters are automatically launched based on a 911 call. “Once ground responders and the helicopter arrive, sometimes they may find patients who are awake, talking and have viable vital signs,” Delgado said. “The challenge is getting helicopter to patients who need fast but not life-saving transport, because if they can intervene and make a difference, but also know based on certain clinical data that their injuries aren’t serious enough to require air transport.”

Most health economists in high-income countries, such as the United States, consider medical interventions that yield a year of healthy life a measure known as a quality-adjusted life-year. At a cost of between $55,000 and $100,000 to be cost-effective, Delgado said. If society is willing to pay as much as $100,000 toward helicopter transport for the seriously injured patients, then helicopter transport needs to reduce the mortality rate of these patients by a modest 1.6 percent compared with ground transport to meet this threshold, the study says. Or it needs to improve long-term disability outcomes, the study says.

“If future studies find helicopter transport leads to improved long-term outcomes, survival benefit and cost-effectiveness, then helicopter transport would be considered cost-effective, even if no additional lives were saved,” Delgado said.

“Only a handful of studies have examined outcomes other than death, without definitive results,” the authors write.

“The potential drawbacks hasn’t been clear. More accurately determining which injured patients benefit from the service of biomedicine, among them big data, is going to revolutionize the way we prevent, diagnose and treat disease,” Minor expressed gratification for Stanford’s leadership role in large information-technology corpora-

Stanford/Oxford conference will highlight the role of big data in biomedicine

By Bruce Goldman

A three-day conference, to be held May 22-24 at the School of Medicine’s Li Ka Shing Center for Learning & Teaching, will highlight the burgeoning opportunities for those who can creatively mine the rich veins of data steadily accumulating in biomedical databases.

Those wishing to register for the conference or to learn more about it can do so by visiting http://bigdata.stanford.edu. The event is open to the public.

“We’re bringing together people from academia, industry, government and foundations who want to learn more about how big data can drive discoveries for a healthier world,” said Arul Butte, MD, PhD, chief of systems medicine at Stanford and professor of genetics at Stanford, who is the conference’s scientific program committee chair.

The event, jointly sponsored by Stanford Medicine and Oxford University, will feature 32 speakers representing large information-technology corporations, venture capitalists and academia. Anne Wojcicki, CEO and co-founder of the consumer-genomics company 23andMe, and David Duncan, director of the Oxford Internet Institute, will give keynote speeches.

The conference, to be held at the Stanford Conference Center, will explore the massive amounts of data available for individuals and populations is going to revolutionize the way we prevent, diagnose and treat disease as well as the ways we prevent, diagnose and treat disease. Minor expressed gratitude for the Stanford leaders who gave it their support for the conference.

Butte said, “We expect that attendees will walk away with some understanding of the latest tools and technologies available for studying and using big data in biomedicine, of where the unmet needs are and how they can be addressed with these approaches, and of what the tractable next steps may be that they can take to be pace setters and innovators.”

The cost of the conference, which ranges from $350 for a half-day to $400 for the full three days, includes meals and an evening trip to the Computer History Museum. Registration remains open but seats are filling up fast. Information about special rates at some local hotels is available at the conference’s website. mks
A new method for assessing options for heart-disease surgery

By Rina Shaikh-Lesko

Researchers at the School of Medicine have developed a method of predicting which patients with heart disease would benefit more from angioplasty.

Drawing on Medicare records of more than 100,000 patients with heart disease, the team demonstrated that the apparent effectiveness of heart surgery varies widely based on individual characteristics. The data enabled them to predict which type of intervention — coronary bypass surgery or coronary angioplasty — would benefit more from angioplasty.

The study showed that patients with severe heart disease — those who had two or more blocked arteries — lived longer when they chose to start with a coronary artery bypass surgery instead of angioplasty, but how much longer varied widely. For patients with certain conditions, including diabetes, heart failure, peripheral arterial disease and a recent heart attack, coronary bypass surgery extended their lives by a few weeks to a few months beyond how long they would have been expected to live had they undergone angioplasty. On the other hand, patients without any of these conditions lived longer if they had angioplasty instead of surgery.

Instead of running a randomized clinical trial, which is considered the gold standard for comparing treatments, the researchers simulated a clinical trial using Medicare patient records from 1992 to 2008. One of the drawbacks of randomized clinical trials is that they must be small and often the type of patients who do participate. Hlatky’s method used a much larger and more diverse pool of patients, and the treatments were compared directly among patients using a standard method called propensity score matching.

“We tried to find medical twins,” one of whom got coronary bypass surgery and one of whom got angioplasty — two people who looked alike medically, but were treated differently. The results showed that the outcomes of these well-matched patients were presumably due to the treatment they received rather than other factors like their medical condition, age, race or the part of the country they lived in.

There is growing evidence that some patient characteristics, such as age, sex and diabetes history, make a difference in the effectiveness of coronary surgery, but this is the first study to quantify how many such characteristics contribute, and to develop an assessment tool to help doctors decide on a treatment plan for their patients.

Other Stanford co-authors include Laurence Baker, PhD, professor of health policy and research; biostatistician Sativa Thorne, PhD, MD; and biostatistician David Shulman, PhD. Researchers at the University of California-San Francisco and Kaiser Permanente Northern California were also involved in the study.

The study was funded by the National Heart Lung and Blood Institute. The Department of Medicine and the Department of Health Research and Policy also supported the research.

Firefly protein lights up degenerating muscles, aiding research

By Bruce Goldman

School of Medicine scientists have created a new mouse strain that is designed to express a firefly protein in the muscles in which degenerative muscle disease is most pronounced. The easily observable signal is a visual one, giving doctors a new tool to understand how variation among patients affects various treatments and procedures.

“Firefly protein lights up degenerating muscles, aiding research”

“Insomnia offers much more refined guidance to clinicians,” said Ralph Horwitz, MD, co-chair of a recent Institute of Medicine conference on using routine clinical data to improve medical guidelines. “It would be quite helpful to have medical guidelines that work best for the typical patient.”

Clinicians could identify the individuals in the population who would benefit the most, and target treatments more precisely, they said. “We could have quite good outcomes at much lower cost,” said Hlatky.

Hlatky added that this tool could be used to study other treatments for heart disease, and even for other conditions, such as cancer and stroke.

While this technique cannot be used in humans, it paves the way to quicker, cheaper and more accurate assessment of the efficacy of therapeutic drugs. The new mouse strain is already being employed to test stem cell and gene therapy approaches for muscular dystrophies, as well as drug candidates now in clinical trials. Rando, MD, PhD, professor of neurology and neuroscientific and director of Stanford’s Glenn Department of Neurology and Neurological Science, said the new mouse strain is already being used by researchers to test the effect of gene therapy for muscular dystrophy.

“Muscular dystrophy is a geneti- cally transmitted, progressive condition whose hallmark is degeneration of muscle tissue. There are many different forms, whose severity, time of onset and preference for one set of muscles versus another depend on which gene is affected. But as a general rule, the disease begins to develop well before symptoms show up.”

As the muscle fibers of someone with muscular dystrophy die off, nearby satellite cells — which are normally dormant in adult muscle tissue and only come into play when muscles are damaged or are growing or regenerating — can now be made that are capable of reining in disease progression, researchers like Rando are learning.

In these luminescent mice, we could pick up the disease’s pathological changes well before they could be seen otherwise,” said Rando. “The readout was so sensitive we could observe those changes within a two-week period. Not only that, but we got our measurements instantaneously, without killing the mice.”

The new assay’s speed, accuracy and relative noninvasiveness will advance the pace of drug development.

“It is our hope that this assay will help address the unmet need of a sensitive and specific test for muscular dystrophy as an early marker for disease severity,” Rando said. “And that even if the disease is not detected in this assay, we might gain an insight into potential therapeutic strategies.”

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[i]Mark Hlatky

[ii]Rina Shaikh-Lesko is a science-writing intern in the medical school’s Office of Communication & Public Affairs.
Groundbreaking
continued from page 1

In 1959 the hospital we have now built on that tradition,” said Stanford University President John Hennessy. “In 1959 the hospital we have now was groundbreaking, but that was in 1959. To deliver the high-quality medical care that people expect today, we need to move forward. The new Stanford Hospital will serve the local community, even as its benefits are felt well beyond it — in excellent patient care, the development of innovative therapies and treatments, and the education of tomorrow’s health-care leaders.”

Though the hospital has been in operation for decades, its current building was constructed in 1959 and cannot be brought up to state-mandated seismic standards. In addition, technology has changed dramatically since then, as have the needs of the patients who come to the hospital for care.

Construction of the new hospital is part of the $5 billion Stanford University Medical Center Renewal Project that will bring facilities to current seismic safety standards and support the growth and modernization of the medical center, which comprises Stanford Hospital & Clinics, Lucile Packard Children’s Hospital and the School of Medicine.

Hoover Pavilion has already been renovated as part of the renewal project and now serves as a hub for Stanford’s primary care services. The groundbreaking for the Packard Children’s expansion took place last September. “We are in the midst of biomedical revolution that offers truly dazzling possibilities for improving the human condition, treating and curing disease, relieving suffering and enhancing life and health,” said Lloyd Minor, MD, dean of the School of Medicine. “Here at Stanford Medicine, we seek to lead that revolution, pushing science as far and as fast as possible. But we never lose sight of the overriding reason behind our work — our patients. They are at the core of who we are. Today marks an important transition, one that will give us the physical environment that our patients deserve and a new model for health.”

Construction of the new Stanford Hospital is being funded through a combination of hospital funds, private donations and the support of leading Silicon Valley companies. Fundraising for the project is ongoing, through the Campaign for Stanford Medicine.

“This giant hole, the foundation of the new hospital, is powerfully symbolic and marks a vision that will change lives,” said Mariann Byerwalter, chair of the hospital’s board of directors, who acknowledged the efforts of the hospital and university boards, faculty, staff, Corporate Partners, community leaders and philanthropists. “It’s a symbol of the combined vision and commitment that brings us here today, and the momentum that will create a transformative new hospital.”

The patients who come to Stanford benefit from deep medical expertise and a commitment to innovation and collaboration, an institutional strength that Bowers, the former patient, emphasized in his remarks. “I and my family owe Stanford Hospital & Clinics a debt of immense gratitude for saving my life,” he said. “My story today has been about cancer, but my message is about life, love and hope. The new hospital means that many more patients will be able to survive to tell their own story of life, love and hope.”

“We never lose sight of the overriding reason behind our work — our patients. They are at the core of who we are.”

Construction of the new hospital is part of the $5 billion Stanford University Medical Center Renewal Project, which will bring facilities to current seismic safety standards and support modernization and expansion efforts. The medical center comprises Stanford Hospital & Clinics, Lucile Packard Children’s Hospital and the School of Medicine. Scheduled to open to patients in 2018, the new hospital building will include more beds, private rooms, state-of-the-art operating suites, expanded emergency services and the flexibility the hospital needs to adapt to advancing technologies and more streamlined services.

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Chris Bowers, diagnosed with cancer in 2009, credits Stanford with saving his life. He spoke May 1 at the groundbreaking ceremony.

Shovels were wielded by (from left to right) Mariann Byerwalter, chair of Stanford Hospital & Clinics Board of Directors; Amir Dan Rubin, president and CEO of Stanford Hospital & Clinics; Stanford University President John Hennessey; School of Medicine Dean Lloyd Minor; and Palo Alto Mayor Gregory Scharff.

Photography by Robert Vondridge
**Probable role of Parkinson’s-linked protein revealed**

By Bruce Goldman

Researchers at the School of Medicine have exposed the possible function, in the healthy brain, of a mysterious molecule that has been implicated in Parkinson’s disease, a degenerative disorder of the central nervous system. The discovery, made by using a stripped-down experimental system that mimics key aspects of how nerve cells communicate with one another.

Thomas Südhof, MD, has developed much of his knowledge of understanding the goings-on in the terrifically complex nerve cell from which nerve cells squirt specialized signaling chemicals called neurotransmitters. It is the diffusion of neurotransmitters from one nerve cell to the next that underpins our thoughts, feelings and movements.

“The brain’s activity is no mere mob-action squint-gun melee, though. For our most exhaled organ to do its job, the signals sent by nerve cells must be marked by profound precision, both in their intensity and in their timing. The details of how this occurs are still coming into focus.”

Axel Brunger, PhD, devised a simplified experimental system that captured some of the essential complexity and was looking for interesting problems to solve with it. So he began sitting in on the Südhof lab meetings and was intrigued by the idea of nerve-cell signal transduction — or, perhaps, in disease states, “We’d just developed this new system, and we were scouting our interesting proteins implicated in nerve-cell signal transmission or, perhaps, in disease states,” Brunger said.

Brunger’s experimental system intrigued Jacqueline Burré, PhD, a research assistant in Südhof’s group, who was subjecting a protein called alpha-synuclein to close scrutiny. Alpha-synuclein, a wallflower among the proteins in the brains of Parkinson’s patients and are considered a hallmark of the disease. “We’ve seen it seem to implicate an overabundance of alpha-synuclein as a culprit in Parkinson’s disease, but the truth appears to be more nuanced. Südhof’s group, for example, had created a strain of lab mice lacking the gene for alpha-synuclein and also the gene for two close cousins of that protein, beta- and gamma-synuclein. Burré found that, curiously, these mice seemed to function just fine in the absence of any Greek-letter-prefixed synucleins — at first. The youthful “trouble spots,” as they are known, thrive in their early years, but the presence of synucleins seemed to catch up with them as they aged. The mice eventually developed severe abnormalities in motor function and died much sooner than their normal peers. (Parkinson’s patients develop movement-related symptoms including tremor in the extremities and stiffness.) The effect was analogous to running a car for several years without changing the oil. Despite the lack of immediately visible damage, the long-run effect is almost certainly the engine’s demise. “Lots of people have been looking at what alpha-synuclein does wrong,” said Burré, who shares lead authorship of the April 30 in *Nature* study with biophysicist Jiajie Diao, PhD, a research specialist in Brunger’s group. “Almost no one is looking at what it does normally, in a healthy person or animal. That was our prime focus, and we wanted to know how this works at the molecular level.”

Brunger’s experimental system, in which the rapid-fire molecular events involved in neurotransmitter secretion are pared down to the basics, looked like an excellent way to find out. Nerve cells don’t simply squirt our neurotransmitter molecules out across the synapse, into the complex networks that constitute our brains, every individual nerve cell has a lengthy, sinuous, tubular extension cord, or axon, that hooks up with thousands of other nerve cells. Neurotransmitters are housed within tiny bubble-like packets in the cell. These packets congregate in myriad small, bulbous nozzles dotting the axon, with each bulb abutting a downstream nerve cell. When an electrical impulse travels down the axon on which those bulbs reside, it triggers the fusion of the neurotransmitter-packed packets with the nerve cell’s outer membrane. The packets’ contents then spill into the narrow space separating the bulbs from the nerve cell they abut.

In the first case, the functional alpha-synuclein becomes instrumented in characterizing several proteins — some embedded in the surfaces of all neurotransmitter-loaded packets, and others in the membrane surrounding the cells’ bulbous nozzles — that, in response to electrical impulses coursing through the nerve cell, shift their structures temporarily and, like a living zipper, interact in such a way as to pull the packets and the cell’s outer membrane so tightly together that they fuse and the neurotransmitters are released. Brunger’s bench-top system employs two kinds of synthetic vesicles: very small ones to represent the tiny packets, and others representing the secretory bulbs. In their experiments, the Stanford investigators coated both types of vesicles, respectively, with proteins that are specifically found on the packet or the bulb surfaces and that have been shown to be essential to proper membrane fusion. Substituting a chemical procedure for the electrical impulses that normally elicit these proteins in interactions, the scientists could trigger fusion between the two vesicle types at will. Thus, the system served as a simplified synthetic model of the apparatus of nerve-cell secretion.

Next, the scientists measured how many of the packet vesicles adhered to the surface of the bulb vesicles in the presence or absence of alpha-synuclein. Interestingly, alpha-synuclein’s presence didn’t seem to change the dynamics of the membrane-fusion process itself. Instead, the protein seemed to tether packet vesicles together. “Alpha-synuclein causes the packet vesicles to cluster together at the synthetic cell surface membrane,” said Burré.

After showing that this clustering effect was proportional to the amount of alpha-synuclein added, the team determined that it occurs because one part of alpha-synuclein has an affinity for lipids that are the major constituents of the neurotransmitter-carrying packets’ surfaces, while another part of the molecule binds to a particular protein that, in the experiment as well as in actual nerve cells, was embedded in the surfaces of the packets. This could explain both how a deformation of functional alpha-synuclein resulting from a mutation in the gene coding for it and an over-abundance of alpha-synuclein caused by, among other things, duplication of the gene can cause trouble, Brütsch said. In the first case, the dysfunctional product of the gene fails to induce enough clustering, so that an insufficient number of neurotransmitter-carrying packets are in place (near the transmission bulbs’ surfaces) when they’re needed. In the second case, a hyper-abundance of alpha-synuclein leads to its aggregation, interfering with the correct positioning of the packet vesicles near the transmission bulbs’ surfaces or with their efficient fusion with those surfaces.

“This is exactly what it is happening in the living brain remains to be seen,” cautioned Brunger. “We’re working with a minimal system. We can’t be sure yet if this handful of proteins we’re adding to our reconstituted membranes are enough to recapitulate the natural process.” But both his and Südhof’s groups are actively looking for ways to replicate their findings in brain tissue. Assuming they do, it still won’t necessarily translate into the immediate development of Parkinson’s drugs, Brütsch noted, because ensuring that precisely the right alpha-synuclein levels are present in people’s nerve cells at the right times is tougher than just reducing or increasing levels of this protein. But the scientists say that the more we can learn about alpha-synuclein’s normal function, the better. “You should try to completely understand the normal function of a protein before playing around with it in human subjects,” she said.

Other study co-authors were post-doctoral scholars Sandra Vivona, PhD, Daniel Cipriano, PhD, and Minjoung Kyoung, PhD; and research associate Manu Sharma, PhD.

The study was funded by HHMI and the National Institutes of Health. Stanford’s Department of Molecular and Raul Chaum field also supported this work.

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**The faculty named members of National Academy of Sciences**

Three School of Medicine faculty members were named as new members of the National Academy of Sciences on April 29. The academy is an honorific society that recognizes distinguished and continuing achievements in original research. Ben Barres, MD, PhD, professor and chair of neuroscience, who focuses on glial cells, which constitute 90 percent of the cells in the brain but whose function remains poorly understood. His lab was first to be identifying all the component cells in the developing nervous system and studying their interaction through innovative techniques. Emmanuel Mignot, MD, PhD, director of the Center for Sleep Studies and Medicine, and professor of psychiatry and behavioral sciences. His lab focuses on the neurobiology, genetics and immunology of narcolepsy, a disorder that causes periods of extreme daytime sleepiness, and other sleep disorders. He is recognized as having discovered the gene that causes narcolepsy.

Stephen Quake, PhD, investigator for the Howard Hughes Medical Institute, and professor of bioengineering and of applied physics. Drawing upon his physics background, Quake, who holds the Lee Otterson professorship, has introduced large-scale quantitative approaches in many areas of biology that were previously impossible to address. His innovations include a rapid DNA sequence, a non-invasive prenatal test for Down syndrome and the biological equivalent of the integrated circuit. In addition three other Stanford University faculty members were named foreign associates to 437. Foreign associates to 437. Foreign associates to 437.

The new members will be inducted next April during the academy’s 151st annual meeting in Washington, D.C. 
Linda Boxer officially steps into her new role as vice dean on Sept. 1.

By Ruthann Richter

Linda Boxer, MD, PhD, a distinguished clinician, educator and researcher at the School of Medicine, has been named the school’s new vice dean. Boxer, a professor of hematology, is chief of the Division of Hematology and senior vice chair of the Department of Medicine, where she also serves as interim chair from August 2010 to June 2012. “During her time as interim chair, Linda quickly won the admiration and respect of faculty, trainees and staff, dramatically improving communication and mentoring, as well as expanding educational opportunities for residents and students,” said Lloyd Minor, MD, dean of the medical school. “I have been most impressed by Linda’s integrity and insight and am honored to have her join our senior leadership office.”

The appointment is effective Sept. 1, though Boxer already has begun transitioning into her new role. As vice dean, she will represent the strategic priorities for the school, provide guidance on senior academic leadership appointments and work to increase collaboration between the basic and clinical science departments, as well as with the hospitals and the university at large.

“As the senior official in academic affairs, she will be responsible for faculty recruitment, appointment, retention and promotion of all faculty members,” Boxer said. “We have the opportunity at Stanford to create the future of medicine in all three of our missions: research, clinical care and education. I look forward to working with Lloyd and the other leaders of Stanford Medicine and the university along with the members of the faculty, the staff and trainees to help guide Stanford to an even greater level of excellence.”

David Stevenson, MD, professor of pediatrics and director of the John逊 Center for Pregnancy and Newborn Services at Lucile Packard Children’s Hospital, is the current vice dean, a position he has held for the last seven years. He also served as senior associate dean for academic affairs for the last two years.

“With wisdom and compassion, he has provided a supportive environment in which faculty can develop, flourish and succeed during each stage of their career at Stanford,” Minor said. He said Stevenson had been instrumental in establishing the Office of Diversity and Leadership, in obtaining principal investigator status for the Medical Center Line faculty and in creating the internal training program in hematology/oncology.

“Linda quickly won the admiration and respect of faculty, trainees and staff,” Boxer trained at Stanford, where in 1981 she earned both a medical degree and a doctorate in biophysics. One of her mentors at Stanford was hematologist Stanley Schrier, MD, professor emeritus of medicine, who inspired her to specialize in the field of hematology and oncology, she said. She was at first reluctant to become an oncologist because cancer is such a difficult disease to treat, and she was afraid she would have to say goodbye to many patients. But she said she found her colleagues in the field extremely empathetic and the intense relationships with patients and families very rewarding.

“During her time as interim chair, Linda quickly won the admiration and respect of faculty, trainees and staff.”

Boxer said she also finds teaching and mentorship gratifying; she is the former director of the fellowship training program in hematology.

“What is the most important thing we do?” she said in a March 2011 interview. “I think it really is preparing the next generation of physician scholars and leaders.”

Boxer also maintains a research lab focusing on the molecular abnormalities that occur in blood cancers. She is a member of Bio-X and the Stanford Cancer Institute.

Vindol Menon is senior author of a study involving 8- and 9-year-olds that found the size and wiring of specific brain structures predicted how much an individual child would benefit from math tutoring.

Math continued from page 1

is going to learn during eight weeks of math tutoring based on measures of brain structure and connectivity,” said Vindol Menon, PhD, the study’s senior author and a professor of psychiatry and behavioral sciences. Menon is also a member of the Child Health Research Institute at Lucile Packard Children’s Hospital.

“The results are a significant step toward the development of targeted learning programs based on a child’s current as well as predicted learning trajectory,” said the study’s lead author, Kaustubh Supkar, PhD, postdoctoral scholar in psychiatry and behavioral sciences.

Menon’s team focused on third-grade students ages 8 and 9 because these children are at a critical stage for acquiring basic arithmetic skills. The study included 24 third-graders who participated in a well-validated program of 15 to 20 hours of individualized math tutoring over eight weeks. The tutors explained new concepts to children and also got them to practice math skills with an emphasis on speed, and the sessions were tailored to each child’s level of understanding.

Before tutoring began, the children were given several standard neuropsychological assessments, including tests of IQ, working memory, reading and math-problem-solving abilities. Both before and after the eight-week tutoring period, children’s arithmetic performance was tested, and all children had structural and functional magnetic resonance imaging scans performed on their brains.

To control for the effects of math instruction the children received at school (rather than during tutoring), a comparison group of 16 third-grade children who did not receive tutoring, but who had the same testing and brain scans before and after an eight-week interval, was also included in the study.

All 24 children receiving tutoring improved their arithmetic performance. Their performance efficiency, a composite measure of accuracy and speed of problem solving, improved an average of 67 percent after tutoring. But individual gains varied widely, ranging from 8 percent to 198 percent improvement. The children who did not receive tutoring did not show any change in arithmetic performance during the study.

When the researchers analyzed the children’s structural brain scans, they found that larger gray matter volume in three brain structures predicted greater ability to benefit from math tutoring. (The predictions were generated with a machine learning algorithm, the same type of data-analysis tool used to create movie recommendations for users of websites like Netflix, for example.)

Of the three structures, the best predictor of how much an individual child would benefit from tutoring was a larger hippocampus, a structure traditionally considered one of the brain’s most important memory centers. Functional connections between the hippocampus and several other brain regions, especially the prefrontal cortex and basal ganglia, also predicted ability to benefit from tutoring. These regions are important for forming long-term memories.

“The part of the brain that is recruited in memories for places and events also plays a pivotal role in determining how much and how well a child learns math,” Supkar said.

“One of the neuropsychological assessment scores, such as IQ or tests of working memory, could predict how much an individual child would benefit from tutoring,” Menon said. “The brain systems highlighted by this study — including the hippocampus, basal ganglia and prefrontal cortex — are different from those previously implicated in math learning in adults, the researchers noted. When solving math problems, adults rely on brain regions that are specialized for representing complex visual objects and for processing spatial information.

And the findings suggest that the tutoring approach used, which was tailored to each child’s level of understanding and included positive, high-speed arithmetic practice to help cement facts in children’s heads, works because it is compatible with the way their brains encode facts.

Memory resources provided by the hippocampal system create a scaffold for learning math in the developing brain,” Menon said. “Our findings suggest that, while conceptual knowledge about numbers is necessary for math learning, repeated, speeded practice and testing of simple number combinations is also needed to encode facts and encourage children’s reliance on retrieval — the most efficient strategy for answering simple arithmetic problems.” Once kids are able to pull up answers to basic arithmetic problems automatically from memory, their brains can tackle more complex problems.

A researcher’s next steps will include comparing brain structure and wiring in children with and without math learning disabilities, analyzing how the wiring of the brain changes as children grow, and determining whether lower-performing children’s brains can be exercised to help them learn math.

“We’re pushing a very ecologically relevant model of learning,” Menon said. “Academic instruction should rely on validated instructional principles while incorporating individualized training to provide feedback on whether students are right or wrong, how they’re wrong and how they can improve their math skills.”

Other Stanford co-authors included social science research assistant Anna Snaugter and Linda. Stanford was funded by the National Institute of Child Health and Human Development. Stanford’s Department of Psychiatry and Behavioral Sciences also supported the work.
Nuclear-power industry’s lessons for health care

At first blush, the health-care and nuclear-power industries don’t appear to have much in common. But if you look closely, leaders in both industries are working to achieve milestones that involve the ability to communicate directly through their respective membranes, thus narrowing the gap between the two. These similarities have been pointed out repeatedly in the literature, highlighting the potential for learning and cross-pollination.

Our participants in this unusual collaboration was David Gaba, MD, professor of anesthesiology and the anesthesia and intensive care in experimental and computational models at the University of California, San Francisco, and anesthesiologist at the Department of Veterans Affairs.

One of the areas of overlap was the use of simulation technology. Both industries have used simulation technology extensively in their training programs, and both have seen significant benefits.

While simulation technology has been used extensively in the health-care industry, the nuclear industry has lagged behind in adopting this technology. However, in recent years, there has been a growing interest in using simulation technology in the nuclear industry to improve safety and efficiency.

In the health-care industry, simulation technology has been used in a variety of ways, including to train nurses and doctors, to improve patient safety, and to develop new procedures.

The nuclear industry has also seen the benefits of simulation technology, but the adoption has been slow. However, in recent years, the trend has been toward increased use of simulation technology in the nuclear industry.

In both industries, the goal is to create a safer and more efficient environment for patients and workers. The use of simulation technology can help achieve this goal by allowing for training and practice of procedures in a safe and controlled environment.

In conclusion, the nuclear-power industry and the health-care industry have much to learn from each other. The benefits of simulation technology in both industries can lead to improved patient safety, increased efficiency, and better outcomes for both patients and workers.

1 Nuclear power and health care don’t seem to have any natural affinity. What common factors do they share?

Both of these industries have human beings operating powerful systems and technologies that ordinarily provide great benefit to humankind, but, if they go wrong, or if the workers are not careful enough, can have negative consequences. The nuclear industry has had to deal with these issues for many decades, while the health-care industry is only now beginning to face the challenges of operating dangerous systems.

2 In the monograph, you address the issue of human factors and how this can influence outcomes. Can you talk more about this issue?

Human factors is the field that studies such issues as stress, memory, and decision-making. In both industries, human factors play a critical role in determining the outcomes of operations. In the nuclear industry, human errors can have serious consequences, while in the health-care industry, they can have serious consequences for patients.

3 What are some of the key things that can health-care providers learn from their colleagues in the nuclear industry?

One big one is the need for standard operating procedures, where possible, which also retain flexibility as needed. A study by the Department of Health and Human Services found that once established, the use of written protocols is a mainstay in this setting. Health care has long depended largely on the individual or the team participating in the event.

4 How might patients ultimately benefit from this collaboration?

Nuclear power has been incredibly safe in the United States. I am not sure how a non-worker has ever been killed by the direct effects of nuclear power production. Sadly, there are still on the order of 100,000 workplace fatalities in the United States each year, including many in the health-care industry due to errors or adverse events. With the use of simulation technology, there are less likely to be errors in the nuclear industry, and others, that we can adapt to our own practices in patient care. We don’t have to be “like” nuclear power, we only have to learn useful things from their experience.

Incidentally, the nuclear-power participants found plenty of things in health care that they thought were not used all that much to their advantage. We can only at this point try to improve our own practices.
Symposium focuses on approaches to improving global health

By Kris Newby

If extreme poverty is a disease, then smart phones are the cure.

That was the message delivered by economist Jeffrey Sachs, PhD, director of The Earth Institute at Columbia University and author of the bestselling book *The End of Poverty*. Sachs was the keynote speaker at the C-IDEA global health symposium, held on April 24 at the Stanford School of Medicine.

C-IDEA is the acronym for the Consortium for Innovation, Evaluation, and Action, a group of Stanford organizations that aim to advance the development of products, services and processes for improving global health.

Extreme poverty kills because of a lack of connections to basic needs, such as good medical care, clean water and medicine, said Sachs. Inexpensive smart phones can connect people in isolated rural villages to all of these essentials.

Invisible to most Americans is the explosive and transformative growth of mobile phone use in Africa. For example, a little over a decade ago, there were only about 100,000 phone lines in Nigeria, Sachs said. Today Nigeria has almost 100 million mobile phone lines. Essentially, smart phones have become the PCs of Africa.

Sachs’ call to action for the packed hall of global health innovators was this: The developing world needs you to create the middleware and information technologies that will build a health-care bridge between the haves and have-nots.

The symposium also featured more than 20 poster presentations and several five-minute summaries of low-cost ideas for preventing disease in developing nations, including:

- “EZPZ,” a method for treating latrine waste with alkalizing lime in Cambodia, so that pathogens that might leak into the water supply can be eliminated and the waste can be recycled as crop fertilizer. (Peter Mul- ligan, PhD, a graduate research assistant in chemical engineering)
- “Fieldscope,” a rugged, inexpensive microscope made of folded paper that can be mass-produced and used for diagnosing malaria and tuberculosis in rural Africa and Southeast Asia. (Manu Prakash, PhD, assistant professor, bioengineering)
- A novel DNA vaccine for Chagas disease, a tropical parasitic disease caused by the protozoan *Trypanosoma cruzi*, which afflicts more than 10 million worldwide. This experimental vaccine will soon be tested in large animals. (Susanna Wen and Izumi Hinkson, graduate students affiliated with SPARK, a medical school program to advance cost-effective ways of translating academic discoveries into drugs or diagnostics)
- Sachs is also a United Nations adviser and champion of the Millennium Villages project, an effort to pilot-test simple medical, educational and agricultural solutions in poor African communities. He used the podium to propose to audience members “here in the heartland of innovation” to use Millennium Villages as test sites for their inventions.

C-IDEA and its global health symposium are initiatives led by Michele Barry, MD, senior associate dean for global health. Supported by a $8 million grant from the National Institutes of Health, C-IDEA has funded, in less than three years, 55 projects in 10 countries. C-IDEA supports global health projects led by students and faculty across the university, through programs such as Bodesign, SPARK, Liberation Technology, the Program for Healthcare Innovation at the Stanford Graduate School of Business, and the “Design for Extreme Affordability” course offered at the Hasso Plattner Institute of Design at Stanford.

Lloyd Minor, MD, dean of the School of Medicine, who also spoke at the symposium, praised Barry’s C-IDEA initiative: “Because of the passion you bring to this endeavor, it’s going to help us maximize our impact in this important area of global health.”

Michele Barry leads the C-IDEA consortium, whose April 24 symposium featured Jeffrey Sachs, right, as the keynote speaker.


differentiation.

- Logistics and supply-chain management
- Text-based patient reminders
- Natural disaster response systems
- Low-cost gene sequencing
- Social media health awareness
- Electronic medical payments
- Online medical training
- Electronic medical records
- Patient self-monitoring and biofeedback
- Community-based diagnostics
- Online medical payments
- Community microscopy
- Low-cost scanning and imaging
- Electronic medical training
- District planning tools
- Low-cost gene sequencing
- Social media health awareness
- Online medical training
- Electronic medical records
- Patient self-monitoring and biofeedback
- Community-based diagnostics
- Text-based patient reminders
- Natural disaster response systems
- Collaboration, and is the co-principal investigator of the NICHD Maternal-Fetal Medicine Units Network.

\[ \text{Yasser El-Sayed} \]

**Brain teaser**

High-school students examine brain tissue samples in the Alway building under the guidance of Hung Ho, a doctoral student in Stanford’s neuroscience program. The students were among some 140 Bay Area high schoolers who came to Stanford on April 19 to participate in Med School 101, an annual, daylong event designed to expose young minds to medicine and related fields. The event is organized by the medical school’s Office of Communication & Public Affairs and sponsored by Stanford Hospital & Clinics.

**Robert Haile**

**Ngan Huang**

**Suzanne Pfeffer**

**Yasser El-Sayed**