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Team designs new model for stroke care

By Kris Newby

Every two seconds, on average, someone on the planet suffers a stroke. For these people, life or death hinges on a precise choreography of health-care workers and machines, all working to restore blood flow to injured brains.

Now, a new stroke care delivery model, developed by researchers at the Stanford Clinical Excellence Research Center, offers evidence-based strategies that enable clinics and hospitals to improve outcomes for stroke patients while at the same time lowering costs related to their care. The main components of the new stroke care delivery model include the following:

• Better stroke prevention by coaching at-risk patients to take preventive medications and to make lifestyle changes.
• Reduction of unnecessary hospital admissions of low-risk, transient ischemic attack patients by setting up TIA outpatient clinics for urgent evaluation.
• Reduction of prolonged hospital stays for mild ischemic stroke patients through a more efficient, 24-hour protocol for in-hospital stroke care.
• Redesign of emergency care to more rapidly administer the clot-busting tissue-plasminogen activator, or tPA, to all eligible ischemic stroke patients.
• Reduction of hospital readmissions by improving the transition of stroke patients to post-hospital care in the community.

The research team estimates that implementing all its recommendations would significantly improve patient care and reduce U.S. health-care costs by up to $1.6 billion per year. The care model and its potential cost savings were described in the Oct. 22 issue of Stroke.

“Our nation needs to find ways to safely treat more patients for less money,” said Arnold Milstein, MD, the center’s director, who helps shape national health policies. “Our center’s innovative care models provide clinicians and administrators with a road map to improving patient outcomes while simultaneously responding to this national imperative.”

Design method

Launched three years ago, the Clinical Excellence Research Center assembles small teams of physicians, business scholars, engineers, and management and social scientists to redesign care delivery for some of the most expensive disease conditions in the United States. In 2012, three fellows — Lucy Kalanithi, MD; Waimei Tai, MD; and Jared Conley, PhD, MPH — targeted strokes, the nation’s leading cause of disability, with an annual national price tag of $26.0 billion in direct health-care spending. (Another team worked on strategies for transitions of chronically ill young adults from pediatric to adult care.)

“We recruit creative young scholars into our center, introduce them to some of the most progressive thinkers both inside and outside of health care, then challenge them,” said Arnold Milstein, the center’s director. “Our nation needs to find ways to safely treat more patients for less money.”

“Therapeutic reprogramming’ may help in treatment of blistering skin disease

By Krista Conger

Induced pluripotent stem cells made from patients with a form of blistering skin disease can be genetically corrected and used to grow back healthy skin cells in laboratory dishes, researchers at the School of Medicine have found. They’ve termed the new technique “therapeutic reprogramming.”

The skin cells formed normal human skin when grafted onto the backs of laboratory mice, they said.

The findings represent a major advance in the battle against the disease, epidermolysis bullosa, in which the top layer of skin, called the epidermis, sloughs off with the slightest friction, leaving open wounds that are difficult to heal. Severely stricken children who survive into their late teens or early 20s often die from invasive squamous cell carcinoma, a skin cancer that can arise during repeated cycles of skin wounding and healing.

“Epidermolysis bullosa is a truly horrible, debilitating skin disease in which the top layer of skin is not properly anchored to the underlying layers,” said Anthony Oro, MD, PhD, professor of dermatology. “When they are born, the trauma of birth rips away their skin, and they continue to suffer severe skin wounds that require constant bandaging and medical attention throughout their lives.”

Stanford has one of the largest epidermolysis bullosa clinics in the world, with an extremely active and engaged population of patients and their families eager to help researchers. The Stanford Department of Dermatology has been working to find new treatments for the disease for over 20 years. The latest advance, in which researchers replaced the mutated, disease-causing gene in the donor-made induced pluripotent stem cells with a healthy version, was funded by an $11.7 million grant from the California Institute for Regenerative Medicine.

New avenue of treatment

“This treatment approach represents an entirely new paradigm for this disease,” said Anthony Oro, MD, PhD, professor of dermatology. “Our nation needs to find ways to safely treat more patients for less money.”

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‘Big data’ approach helps pinpoint possible new stent drug

By Tracie White

School of Medicine researchers hunting for a better drug coating for coronary stents, the small mesh tubes used to prop open plaque-filled arteries, have pinpointed a cancer drug as a possible candidate.

In mice, crizotinib helped prevent stent disease, the often-serious medical problem caused by stents themselves, without affecting the blood vessel lining. The medication has already been approved by the U.S. Food and Drug Administration for chemotherapy.

A paper describing the findings was published online Nov. 17 in the Journal of Clinical Investigation. “This could have major clinical impact,” said Euan Ashley, MD, senior author of the study and associate professor of cardiovascular medicine and of genetics. “We found the agent crizotinib not only reduced stent disease but also protected the endothelium of the blood vessels. The implications are that, down the road, patients who receive drug-eluting stents with this new drug may no longer be required to take blood thinners after their procedure.”

Euan Ashley and his colleagues have identified what they believe would be a better drug for use on stents that prop open clogged heart arteries.

The power of big data

The study is also an example of scientists harnessing vast quantities of data to understand genetically complex diseases. By combining text analysis of the whole medical literature with data from large-scale genetic studies in humans, the researchers built a theory that then they tested in the laboratory.

“We used human tissue to identify novel mediators of disease using the computational biology approach — the ‘big data’ approach,” said Ziad Ali, MD, PhD, lead author of the paper. Ali was a cardiovascular fellow at Stanford during the first years of the study and now is associate director of translational medicine at Columbia University Medical Center.

The computational biology approach can give you a good hypothesis, but then you need to prove it in the lab,” he added. “The marriage of the two is what makes this really special.”

In order to find a more effective drug to use on stents, the researchers first wanted to better understand the genetic pathways of coronary artery disease, also known as coronary athero-sclerosis. The disease is caused by the buildup of plaque along the inner walls of heart vessels. The buildup can eventually lead to chest pain and potentially lethal heart attacks. It is the leading cause of death worldwide.

Balloon angioplasty is a common treatment for atherosclerosis. It’s used to open up a clogged artery, often in combination with the placement of a stent that helps keep the artery open. But stent disease, or in-stent restenosis, is the major limitation to this treatment. This occurs when the stents themselves damage the artery lining, causing the growth of scarlike tissue that narrows the vessels. Such narrowing can lead to recurrence of symptoms and even heart attacks.

The risks of drug-eluting stents

To solve this problem, drug-eluting stents are used to block such growth. But these stents also can inhibit the regrowth of the lining of the blood vessel, the endothelium, leading to delayed arterial healing and increasing the risk of blood clots and heart attacks. Thus, patients treated with drug-eluting stents, a total of 1 million each year nationally, according to the American Heart Association, require longer treatment with blood thinners to prevent sudden stent blockage from a blood clot. This makes drug-eluting stents less desirable for people with bleeding problems or those who will need some type of surgery within a year after the stent.

“Even though we’ve made drug-eluting stents, still 10 percent of stents block up,” Ali said. “Patients have to take a blood thinner for about a year. A lot of our patients’ population is on the elderly side with bad hips or diabetes. Once you get a drug-coated stent, you can’t have surgery for a year. And if you stop the blood thinner, any lesion you’re treating starts clotting off. And that actually causes a heart attack. Stent thrombosis has a high mortality rate.”

“Our idea was to find a novel therapeutic that would stop the regrowth while not affecting the endothelium of the vessels,” Ali said.

Zeroing in on genes

To study the genetic pathways involved in coronary artery disease, researchers started with a gene network analysis of coronary artery samples collected from 89 patients in Germany. Their analysis found that the gene GPX1 is associated with cardiovascular events. GPX1 is one of the body’s strongest natural antioxidant defense mechanisms. They further tested this by studying ROS1-positive lung cancers — to mice with coronary artery disease and surgically implanted stents. They found that the drug stopped stent disease and didn’t damage the endothelial growth.

The major finding of the study is that artery stent disease acts surprisingly like a tumor in the blood vessel wall,” Ashley said. “Inhibiting it with non-specific pharmacological agents, as we do now, leads to heart attacks from clots caused by lack of endothelial lining on the surface of the stent, whereas targeting it with the drug we use here, crizotinib, acts much more specifically and inhibits the disease without side effects.”

These results also highlight the need for targeted rather than broad-spectrum therapies, the study says. Other Stanford co-authors are Vincenzo de Jesus Perez, MD, assistant professor of medicine; postdoctoral scholars Ke Yuan, PhD, Stephen Pan, PhD, and Kathia Zalea-Rivera, PhD; research associates Mark Orcholski, Yoko Kojima and Xiaomei Qu; Christopher Adams, PhD, director of proteomics at the Stanford University Mass Spectrometry Laboratory; Nicholas Leeper, MD, assistant professor of vascular surgery; and Thomas Quertermous, MD, professor of cardiovascular medicine.

The study was funded by the National Institutes of Health, the Netherlands Heart Foundation, the Inter-university Cardiology Institute of the Netherlands, the Dutch Center for Cardiogenetic Research, the Center for Medical Systems Biology and the 7th Framework Program.

Stanford’s Department of Medicine also supported the work.

Better communication between caregivers reduces medical errors

By Erin Digitale

Miscommunication among caregivers is one of the largest causes of medical errors, but a new study suggests that the problem is at least partly preventable.

The children’s hospitals, led by Boston Children’s Hospital and including Lucile Packard Children’s Hospital Stanford, tested the effects of a standardized method for medical residents to hand off information about their patients at shift changes. Shorter shifts for residents have increased the number of such handoffs, prompting increased scrutiny of what happens during them.

“This focus is not unique to medicine,” said Lauren Destino, MD, clinical assistant professor of pediatrics at Stanford. “The link between handoff communication and safety has been demonstrated in industries such as nuclear power, emergency medical services and the airline industry, she said.

Destino is a co-author of the study, which was published Nov. 6 in the New England Journal of Medicine.

At each participating hospital in the study, medical residents were trained to use an acronym that reminded them what information to share about each patient, and in what order. The handoff acronym includes both oral and written communication, and ended with the person who was receiving the information repeating back a summary of what was shared with the person who gave it.

A study tested the effects of a standardized method for medical residents to hand off information about their patients at shift changes. The program also included other supporting efforts to ensure that the handoff procedure was embedded in the hospital’s culture and did not negatively affect the doctors’ overall workflow.

“We decreased preventable adverse events by 30 percent, without any change in nonpreventable events,” said Destino, who is also a pediatrician at Lucile Packard Children’s Hospital Stanford. “That was a big step forward.”

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Inside Stanford Medicine
Enzyme that fixes broken DNA sometimes destroys it instead, new research shows

By Rosanne Spector

Enzymes inside cells that normally repair damaged DNA sometimes wreck DNA instead, researchers at the School of Medicine have found. The insight could lead to a better understanding of the causes of some types of cancer and neurodegenerative disease.

In a paper published online Nov. 27 in Molecular Cell, the researchers explain how the recently discovered mechanism of DNA damage occurs when genetic transcriptions, composed of RNA, stick to the DNA instead of detaching from it.

Certain enzymes, called endonucleases, are attracted to DNA/RNA hybrids that form when gene transcription goes awry — and they cut the DNA like scissors, dismantling it.

The researchers conducted the study with human cells in culture, using molecular biology techniques to turn off specific genes. This allowed them to induce cells to form the hybrids and to see what would happen when various enzymes were inhibited.

“What we found is when we get rid of these endonucleases, we don’t see the damage,” said Karline Cimprich, PhD, professor of chemical and systems biology and the paper’s senior author. “When those nucleases are present, they cut the DNA in the hybrid.”

Both helpful and harmful

What’s really interesting, said Cimprich, is these same enzymes are noted for fixing DNA damage. “They take part in the repair of DNA lesions from sunlight and certain chemicals, like those found in cigarette smoke,” she said. “But they are also formed by the hybrid of RNA and DNA are similar to those formed in cells damaged by ultraviolet light.”

What researchers believe happens is that the repair machinery misrecognizes these structures and cuts them, she said. She and her colleagues have launched more experiments to figure out why this happens.

The study not only opens up new avenues for understanding DNA damage, it expands the role of the messenger RNA molecule. In the last decade, researchers have discovered that messenger RNA molecules can act like small RNAs, as some of which the research community has been focused on.

“The messenger RNA is known to transmit the information and make the proteins,” said Cimprich. “But we found that if it isn’t removed properly it destroys the DNA that originally encoded it.”

A study published by Cimprich and colleagues in Molecular Cell in 2009 alerted researchers to the importance of RNA in DNA damage. Their genomewide screen to identify factors that help fix DNA damage found hundreds of different molecules, some of which the researchers expected. But most of the molecules were surprises. And most interacted in some way with RNA, which pointed to RNA as a culprit in causing DNA damage.

“When we thought about what would cause DNA damage in cells, we thought about problems with RNA replication and RNA repair,” she said. “But now we’re beginning to see that problems with RNA can also feed back to the DNA.”

Understanding role of enzymes

Now the researchers are trying to understand why some of the enzymes that control transcription are causative in DNA damage, with an eye to understanding the roots of some cancers. “A lot of oncoproteins are transcription factors. We’re looking at whether those cause genomic instability by making hybrids like those we’ve seen. Is this a different route to DNA damage and cancer?” Cimprich said.

“Recent work has also implicated these hybrids in neurodegenerative diseases, including Fragile X syndrome, Friedreich’s ataxia and amyotrophic lateral sclerosis type 4,” said Julie Sollier, PhD, the lead author of the paper and a postdoctoral researcher. “We would like to explore the potential role of the endonucleases we identified in these diseases as well.”

Other Stanford co-authors are graduate student Caro- line Townsend Stork and former graduate student Renee Paulsen, PhD. Researchers at the University of Sheffield contributed to the paper.

The research was supported by the Spanish Ministry of Economy and Competitiveness, the European Union and the National Institutes of Health.

Stanford’s Department of Chemical and Systems Biology, also supported this work.

Errors continued from page 2

suggests that it was the improved handoffs themselves that led to the reduction in errors. “If both preventable and possible harm events had dropped, that might have suggested the hospitals were seeing healthier or safer care and that meets this need for our patients,” Amy Starmer, MD, PhD, professor of chemical and systems biology and the paper’s senior author. “When those nucleases are present, they cut the DNA in the hybrid.”

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Stanford’s Department of Chemical and Systems Biology, also supported this work.

New center established to study human genome regulation

The National Human Genome Research Institute has awarded $15 million to the School of Medicine to establish a Center of Excellence in Genomic Science.

The new center, called the Center for Personal Dynamic Regulomes, brings together an interdisciplinary team of Stanford researchers to create better ways of understanding genome regulation. Each gene has a system of switches that controls when and where a gene will turn on. The regulome is the complete set of switches for all genes.

“People have spent a lot of time making a catalog of sequences, or genetic variants, of genetic switches,” said Howard Chang, MD, PhD, professor of dermatology and principal investigator of the center. “When it comes to actually understanding them, to use them to address a biological problem or make a clinical decision, there’s a final gap that needs to be bridged.”

The center’s goal is to develop new technologies to pinpoint the relevant switches for disease-causing genes in real time using small, human clinical samples, equivalent to a standard blood draw.

Other Stanford investigators involved in the center include Will Greenleaf, PhD, assistant investigator of genetics; Mike Snyder, MD, professor and chair of genetics; Wing Wong, PhD, professor of statistics and of health research and policy; and Alex Urban, PhD, assistant professor of psychiatry and behavioral sciences.

Four medical school professors elected fellows of AAAS

Four professors at the School of Medicine have been elected fellows of the American Association for the Advancement of Science. The honor is bestowed on AAAS members by their peers for meritorious efforts to advance science or its applications.

RUSS ALTMAN, MD, PhD, professor of bioengineering, of genetics and of biomedical informatics research, was elected for contributions in the field of bioinformatics, particularly for analysis of targets for drug action and of the impact of human variation on drug responses. Altman, MD, who holds the Kenneth Fong Professorship, is interested in the analysis of protein and RNA structure and function, as well as in applying systems biology concepts to pharmacology and personalized medicine.

SANJIV “SAMI” GAMBHIR, MD, PhD, professor and chair of radiology and director of the Canary Center for Cancer Early Detection at Stanford, was elected for his work in multimodal molecular imaging of living subjects. In his work, Gambhir, who has a particular interest in cancer biology and gene therapy, combines advances in molecular and cell biology with those of biomedical imaging. He holds the Virginia and D. K. Ludwig Professorship in Cancer Research.

MICHAEL SNYDER, PhD, professor and chair of genetics, was elected for contributions to the field of genomics, particularly for inventing or pioneering technologies to pinpoint chromatin-immunoprecipitation sequencing, RNA sequencing, tiling array, protein microarray and personalized medicine technology. Snyder, who is the Stanford W. Ascherman, MD, FACS, Professor in Genetics, has been deeply involved in international, multi-institutional efforts seeking to understand and compare the DNA elements controlling gene expression in humans and other model organisms, such as mice.

WILLIAM TALBOT, PhD, professor and chair of developmental biology, was elected for his work using zebrafish to understand the development of myelinated axons in the vertebrate nervous system. This process is associated with many human diseases, including multiple sclerosis. He and his lab have used genetic screens to identify several genes with specific functions in myelination. They hope to define new zebrafish models of important myelin disorders in humans and to develop new therapeutic options for myelin repair and prevention of axonal damage after demyelination.

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Karline Cimprich

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Lymphedema home treatment improves outcomes, reduces cost

By Tracie White

Patients with swelling caused by cancer-associated lymphedema can both reduce the severity of the disease and the overall cost of medical care by taking therapeutic steps at home, according to a study by researchers at the School of Medicine.

The study looked at the prevalence of lymphedema, a common side effect of cancer treatments, and found that the average annual cost of care for a patient with the condition decreased from $62,190 to $50,000 a year when the patient used pneumatic compression devices to treat the swelling.

"Total health-care costs for these patients are very high, but can be lowered significantly with effective treatment intervention, in this case a compression device," said Stanley Rockson, MD, professor of medicine and lymphatic medicine, and Stanford senior author of the study, which was published online Dec. 3 in PLOS ONE. "Pneumatic compression devices may be a compelling argument for increased use of similar home-care devices to reduce costs."

The first author of the study is Kimberly Brayton, MD, JD, a former cardio-vascular fellow at Stanford.

Lymphedema is most commonly caused by the removal of or damage to lymph nodes as a part of cancer treatment. It results from a blockage in the lymphatic system, which is part of the immune system. The blockage prevents lymph fluid from draining well and the fluid builds up, leading to swelling, which can be painful and debilitating. These symptoms can be controlled with various treatments, including treatments done at home and outpatient physical therapy. Home treatments for lymphedema include manual lymphatic massage, multilayer bandages and regular compression garments, which reduce tissue fluid.

For years, scientists have considered the laboratory mouse one of the best models for researching disease in humans because of the genetic similarity between the two mammals. Now, researchers at the School of Medicine have found that the basic principles of how genes are controlled are similar in the two species, validating the mouse’s utility in clinical research.

However, there are important differences in the roles of gene regulation that distinguish us as a species. A large majority of the genes that are identical between a mouse and a human, but we would argue how they’re regulated is quite different,” said Michael Snyder, PhD, professor and chair of genetics at Stanford. “We are interested in what makes a mouse a mouse and a human a human.”

In 2003, the National Institute of Health’s Mouse ENCODE, was meant to complement a project called the Encyclopedia of DNA Elements, or ENCODE, that began in 2003. ENCODE studied specific components in the human genome that guide genes to code for proteins that carry out a cell’s function, a process known as gene expression. Surrounding the protein-coding genes are non-coding regulatory elements, molecules that regulate gene expression by attaching proteins, called transcription factors, to specific regions of DNA.

Why mice matter

Mouse ENCODE analyzed more than 100 mouse cell types and tissues to annotate the regulatory elements of the mouse genome and compare them to the regulatory elements in the human genome. Both ENCODE and Mouse ENCODE are funded and coordinated by the National Human Genome Research Institute. Because mice are used as model organisms for many human clinical studies and drug discovery, understanding how gene expression works in mice allows researchers to understand how the results found in mouse studies can translate to humans.

“The thought is when you compare things, it helps to understand genome annotation,” said Mark Gerstein, PhD, the Albert L. Williams Professor of Biomedical Informatics at Yale University. “It’s making the mouse and human similar organ models.” Gerstein collaborated on previous ENCODE research but is not part of the Mouse ENCODE consortium, which is composed of researchers from more than 30 institutions.

Snyder is a co-senior author of the main paper — which was published in Nature on Nov. 19 — that describes the overall findings of the project, and of two companion papers (one published in the same issue of Nature, the other published online Nov. 17 in the Proceedings of the National Academy of Sciences) that explain individual components of the project.

Stanford postdoctoral scholars Yong Cheng, PhD, and Zhizhao Ma, PhD, are co-leader authors of the Nature companion paper. They identified where 34 transcription factors attach to the DNA strand to control gene expression on regions called binding sites.

Details differ

“Transcription factors are kind of like people: They work together in many different situations to execute certain tasks,” said Snyder, who holds the Stanford W. Ascherman, MD, FACS Professorship in Genetics. “What we discovered is that the general principles are the same in mice and people, but the details are quite different. In general, the mouse factors are binding at different locations than the human ones in terms of the exact gene targets.”

The researchers’ abundant data is a valuable resource for others studying disease-related genes in mice. They can use the Mouse ENCODE data to see whether the transcription factors regulating their studies’ gene expression are the same or different in humans.

“If you focus on a gene that is similar to humans, the result should be easier to transfer from mouse to human,” said Cheng. “But if you’re working on a gene that is different, you need to pay more attention to whether this result can be successfully applied to the human subjects.”

Yiing Lin, MD, PhD, MHS, postdoctoral scholar and clinical instructor in cardiovascular medicine, was co-lead author of a companion paper published in the Proceedings of the National Academy of Sciences along with Yiing Lin, MD, PhD. The study compared gene expression profiles across 15 tissue types in humans and mice.

They found that gene expression profiles in mouse tissues are more similar to one another than to their human counterparts, in terms of the way genes are expressed, a mouse liver is more similar to a mouse kidney than to a human liver, Snyder said.

Understanding the fundamentals

“The mouse is the premier organism for modeling human disease and many other things — a lot of what we know about human biology comes from the mouse,” Snyder said. “The genome is what controls everything at some level. We’re interested in trying to understand the basic processes about how they’re either the same or different across some of the most important species people are studying. It’s just fundamentally important.”

Other Stanford authors of the main study published in Nature are bioinformatics analyst Venkat Malladi and former student Alan Boyle, PhD, Ghia Euskirchen, PhD, Triputi Kawi, PhD, and Anshul Kindaje, PhD.

The main study published in Nature was funded by the National Institutes of Health, the Spanish Plan Nacional, European Research Council, National Science Foundation Graduate Research Fellowship, the Wellcome Trust National Human Genome Research Institute, and the European Molecular Biology Laboratory. The companion paper published in Nature was funded by the NIHORI and the American Recovery and Reinvestment Act.

The companion paper published in the Proceedings of the National Academy of Sciences was supported by the NHGRI; the Common Fund of the Office of the Director of the NIH; the National Cancer Institute, National Heart, Lung, and Blood Institute; National Institute on Aging; National Institute of Mental Health; National Institutes of Neurological Disorders and Stroke; National Disease Research Interchange; Roswell Park Cancer Institute; Science Care; the Broad Institute; Van Andel Institute; University of Miami; University of Geneva; University of Chicago; University of North Carolina-Chapel Hill; and Harvard University.

Stanford’s Department of Genetics also supported this work. See also Lisa Marie Potter is a science-writing intern for the medical school’s Office of Communication & Public Affairs.

A collaborative research effort compared regulatory elements of the mouse genome with those of the human genome. “We are interested in what makes a mouse a mouse and a human a human,” Michael Snyder said.
Physician who treated Ebola patients emerges from quarantine

By Ruthann Richter

After 21 days of home isolation, Stanford emergency physician Colin Bucks, MD, emerged Nov. 14 to a hero’s welcome, besieged by well-wishers and health professionals around the world eager to learn from his experience of treating Ebola patients in West Africa.

Bucks said he feels he left a big part of himself behind with the patients and staff still grappling with the deadly disease at the remote jungle clinic in northeast Liberia, where he volunteered for a month.

“My heart is still there because I know how hard they’ve been working,” he said during a rare break between meetings and phone calls. “I’m always thinking, ‘How is it going? Were they able to accomplish something we’d hoped to accomplish? And how are my friends — the Liberian staff — holding up?’

A volunteer with the International Medical Corps, Bucks treated some 130 patients with Ebola at the clinic. For weeks after his return, he tracked the clinic’s database of his patients to see who lived and who died. He said it’s always hard to lose a patient, whether in Liberia or California, though the losses in Liberia have been high, with dozens of fresh graves filling a two-acre plot near the treatment site.

“It’s natural to be up at the mortality. You just have to turn that energy into the next step — what you can do to improve the care,” said Bucks, clinical assistant professor of surgery at the School of Medicine.

Though precise figures aren’t yet available, he said the care provided at the clinic surely saved lives. “Our gut sense was that we were making a difference — we believe our care procedures to prepare for the unlikely event that a patient with major organ failure, as the prospect of infection was too great and the odds of survival too small at that stage of disease.

And clinicians did not respond to a “code” to revive a patient with major organ failure, as the prospect of infection was too great and the odds of survival too small at that stage of disease.

He said the caregivers focused as much on providing emotional and psychological support as physical care. “For the patients who arrived there, it’s a completely alien place. We were very cognizant of that adjustment and what they were going through. We had dedicated mental health specialists helping patients and families. They had a tough job,” he said. “I had a spectrum of human emotions. I got the uplifting stuff, the daily mundane stuff and some really sad moments. The psychiatrists and social workers got nothing but the tough stuff, having to inform families and take them to funerals.”

He said he developed friendships with the Liberian gravestiders who came day after day to bury their community members from different villages with the patients and staff of the gravestiders. They were hard-working characters,” he said, as well as the source of some macabre humor. He said one of them rejecting chocolates, a gift from a foreign film crew. “You’re giving us candy?” he recalled them saying. “Candy is for children!”

Despite the reported decline in Ebola cases in Liberia, he said the 52-bed clinic today remains busy. The facility is upgrading its services, acquiring an ultrasonic machine and new lab equipment and developing better methods for tracking patients, as it’s been difficult to maintain either paper or electronic records in the wet environment.

“The numbers in Liberia are encouraging, but it too early to say that the epidemic is nearing its end. I’m hopeful major public health education has had an impact, especially in the way funerals were conducted, as there was a major spread,” he said. “It’s too easy to be complacent, which would just lead to a rise in the number of cases.”

Working hard in quarantine

Since his return to California, Bucks has been much in demand as a member of a small cadre of clinicians who have had direct experience with Ebola. He’s been working with health professionals at universities and nonprofits around the world who are doing research on new approaches to combating the disease, tracking trends in the epidemic and developing new designs for protective gear, which are cumbersome and stifling, he said.

“The heat stress is massive,” he said. “Your vision is limited. So anything we can do to improve PPE [personal protective equipment] will help improve patient care.

During his quarantine, he said he did not have a moment of boredom; he was on the phone for 15 hours at a stretch consulting with health experts across the country on Ebola preparedness and on the needs in West Africa. (Stanford paid him during this time.) And though health officials checked in with him twice daily by phone during his quarantine — he never showed any symptoms of the disease — he worried he might contract some garden-variety virus that would trigger a major primary health “hallucination.

“I was nervous I’d have some simple virus that would precipitate a multi-million-dollar evaluation,” as the hospital would have to clear out a unit for him while Ebola was ruled out as a possible cause. He has yet to return to clinical duties but is actively involved in his disaster-preparedness work at Stanford Health Care. He is spending a lot of time at the School of Medicine’s Center for Immersive and Simulation-Based Learning, where Stanford Medicine doctors and nurses have been using mannequins to rehearse patient-care procedures to prepare for the unlikely event that a patient with Ebola comes to Stanford.

Global health center offers seed grants for Ebola-related projects

To help contain the spread of Ebola in West Africa, Stanford’s Center for Innovation in Global Health is offering up to $20,000 and $50,000 for research projects aimed at improving patient care and monitoring trends in the epidemic.

“We are hoping that these innovation grants will build upon our Ebola brainstorming session, which involved participants from all the schools at Stanford and created cross-dialogue about bottlenecks in tackling the Ebola epidemic,” said center director Michele Barry, MD, professor of medicine and senior associate dean for global health.

Stanford faculty, students and staff are eligible for the grants, which must be multidisciplinary in nature and involve participants from different disciplines at the university. Proposals could involve development of new diagnostics, repurposing of drugs for treating Ebola, novel methods of examining patients, innovative design models for vaccine and drug trials and new, less burdensome designs for personal protective gear.

The grants could also be applied to broader issues related to the epidemic, such as epidemic modeling and mapping, biosurveillance, the role of governance in the disease spread and issues of health policy and health communications.

Proposals must be submitted by Dec. 10. Submissions should include a project goal and potential outcome, budget, timeline and biographies of all team members. Submit proposals to Andrea Sprockett at andrea.sprockett@stanford.edu. For more information, visit http://globalhealth.stanford.edu.

Lymphedema continued from page 4

showed that annual costs of medical care decreased from $62,190 in the year prior to the use of the device to $50,000 in the year after they started using the device. During the year following the use of the device, there was a 20% reduction in the need for lymphedema treatments by the patients used all categories of health care, including the frequency of treatment of soft tissue infection, the study said.

“The potential public health implications of these findings are substantial,” Rockson said. “As the American population and lymphedema rates increase, effective home therapies are likely to become increasingly important.”

Stanford’s Department of Medicine also supported the work.
Stroke

continued from page 1

The first step in determining a stroke patient’s course of treatment is to find out if blood-flow disruption is being caused by a clot or a broken blood vessel in the brain. Typically this can be diagnosed through a CT scan of the head. For brain clots, a tPA drug is administered through an IV to dissolve the clot and restore blood flow. Delivery of tPA to patients with broken vessels can worsen the bleeding and be fatal, so care must be taken to make the right diagnosis as soon as a patient arrives.

A neurological team was given our stroke service, we would go to the Helsinki team. It maintains the best door-to-needle-tPA time in the world, with a median time of less than 20 minutes. (The U.S. median is 67 minutes, according to the April 23 issue of the Journal of the American Medical Association.)

The important lesson learned from the Finns — who spent more than 10 years refining their stroke-care processes — is that the key to rapid stroke treatment is to do as much as possible before the patient arrives.

“Every 15 minutes that we cut from the initiation of treatment, an average patient will gain one month of disability-free life,” said Atte Meretoja, MD, one of the architects of the Helsinki stroke care model. In 2012, he implemented the model at the Royal Melbourne Hospital in Australia, bringing median door-to-needle times to 25 minutes, a project that took only four months.

The Helsinki stroke team goes into motion as soon as an ambulance arrives in a probable stroke. Paperwork, test setups and drug orders are initiated before the patient arrives. To achieve this, it is crucial that the ambulance relay patient details to the stroke team. From the emergency bay, patients are wheeled directly on ambulance gurneys to an adjacent imaging room, bypassing the emergency department. (This recommendation is currently not part of the American Heart Association/American Stroke Association Stroke guidelines.) A physician and infusionist stand by the CT scanner, ready to infuse tPA immediately, if appropriate for that patient.

“There is like a clinical ballet, where people have to work together seamless in a busy emergency situation,” said Tai. “The Joint Commission recently approved the implementation of the new CERC care design, 94 percent of suspected stroke patients arriving via ambulance have brain imaging initiated well within national targets, and median door-to-needle time for tPA administration has already dropped by 30 percent. “The Joint Commission just re-accredited our Comprehensive Stroke Center, and they were very impressed with our continuous improvement processes, including the impact that the Helsinki model to Stanford has on our performance,” Tai said.

Innovation in health-care delivery

Though the 2012 CERC stroke fellows initially signed up for a year, all opted for a second year. As the year begins, they are helping the four institutions piloting the model launch various components of the care model.

Today, the fellows feel that their CERC experience has been transformative for them personally and for the health-care industry at large.

“Like many working physicians, everyday I would see need of health-care improvements, both large and small, that weren’t happening,” said Tai. “CERC gave me a way to fix these problems at a national level.”

A number of other CERC care delivery models are entering pilot-testing at 10 sites around the nation. The CERC team is working to recruit more sites to test ways of improving the affordability of high-quality chronic kidney disease care, colon cancer prevention, poor-prognosis cancer care, the transition of chronically ill children to the adult health-care system, and nonemergency surgical care outside of hospitals.

“CERC is an innovation accelerator that increases the flow of new care delivery methods that yield better health with much less national health spending,” said Milstein. “CERC accelerates the flow via three activities: inventing much more cost-effective-care methods for the illnesses that account for the bulk of suffering and spending in the U.S., testing the methods in diverse sites with the support of progressive health-insurers and finding industry partners to spread them nationally.”

Fellows participating in the stroke study were supported in part by the Susan and Dick Levy Fund, a donor-advised fund of the Silicon Valley Community Foundation; and Spectrum, the Stanford Center for Clinical and Translational Research and Education.


Kris Newby is the communications manager for Spectrum, the Stanford Center for Clinical and Translational Research and Education.

Stanford part of a $200 million effort to improve health-care delivery in the United States

By Kris Newby

The Peterson Center on Healthcare, a new nonprofit organization established by the Peter G. Peterson Foundation, has committed $200 million to improve U.S. health care by finding and disseminating ways to improve the quality of care and lower medical spending.

On Dec. 4, the new organization announced its first grant recipients, part of its effort to develop a comprehensive list of best practices across all sectors of the health-care system and beyond.

Identifying features of high-performing primary care practices, Stanford University’s Clinical Excellence Research Center has identified features distinctive of high-quality, patient-centric care at lower-than-average costs. In the accompanying list of best practices, the center will work with other health-care areas, such as medical specialty practices.

A health system performance tracker, The Kaiser Family Foundation created a new web tool that provides dedicated to analyzing the performance of the U.S. health-care system. It provides clear, up-to-date information on trends, drivers and issues that impact the U.S. system, and

personnel working in life-or-death situations, has to be done in a careful, methodical way.

Tai, the neurologist, is managing Stanford Health Care’s transition to the new model. An essential tool in this process is the mock stroke code drill, which Tai and Casal call “dynamic problem solving.” During drills, the team looks for areas where things get bogged down. Problem areas are noted and work-arounds are tested.

For example, the Stanford stroke team shaved a few minutes off the hospital admissions process by having the paperwork people meet patients in the ambulace bay. A few more minutes were saved by putting a sample-collection station in the imaging room.

Casal, the keeper of the stroke team’s performance metrics and a disciple of Toyota’s lean production methods, is pleased with the progress that Tai and colleagues have made since implementation of the new CERC care design, 94 percent of suspected stroke patients arriving via ambulance have brain imaging initiated well within national targets, and median door-to-needle-time for tPA administration has already dropped by 30 percent.

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a means of performance comparison with other countries.

• Strategies for improving health-care data transpar- ency. Patients and providers often have trouble making in- formed decisions about their care because quality and cost Information is not readily accessible or reliable. The Pe- terson Center on Healthcare is collaborating with the Na- tional Quality Forum to bring together leaders from both the public and private sectors to identify specific actions that can be taken to make data and analytic tools more acces- sible to systems that track health-care improvement. The monthly reports will collaborate with stakehold- ers across the health-care system in grant-making, part- nerships and research that contributes to the continual improvement of health-care quality. Its advisory board of health-care researchers and policy leaders includes Arnold Milstein, MD, of Stanford University; Ezekiel Emanuel, the president of the University of Pennsylvania; and Harvey Fineberg, MD, PhD, of the Institute of Medicine. For more information, visit the Peterson Center’s web- site at http://www.petersononhealthcare.org.
Skin

Continued from page 1

A dozen years ago, when Irving Weissman, MD, professor of pathology and of developmental biology at Stanford, headed a National Academy of Sciences panel on stem cells, he raised the possibility that the immune system of a patient who received SCNT-derived cells might still react against the cells’ mitochondria, which act as the energy factories for the cell and have their own DNA. This reaction could occur because cells created through SCNT contain mitochondria from the donated donor and not from the patient. Weissman said that mitochondrial DNA could still look like foreign tissue to the recipient’s immune system, said Weissman, the other co-senior au-thor of the study, said that in his study in the Virginia and Albert Einstein College of Medicine.

That hypothesis was never tested until Schrepfer and her colleagues took up the challenge. “There was a thought that because the mitochondria were on the in-nate immune side, we would not see an immune system reaction,” Schrepfer said. “We found out that this was not the case.”

Schrepfer leads the Transplant and Stem Cell Immunobiology Laboratory in Hamburg, used cells that were created by transferring the nuclei of adult mouse cells into enucleated eggs from genetically different mice. When transplanted back into the nucleus donor strain, the cells were rejected although there were only two single nucleotide substitutions in the mitochondrial DNA of these SCNT-derived cells compared to that of the nucleus donor. “We were surprised to find that just two small differences in the mitochondrial DNA was enough to cause an immune reaction,” she said.

“We didn’t do the experiment in humans, but we as-sumed the same sort of reaction could occur,” Schrepfer added.

Until recently, researchers were able to perform SCNT in many species, but not in humans. When sci-entists at the Oregon Health and Science University announced success in performing SCNT with human cells last year, it reignited interest in eventually using the technique for human therapies. Although many stem cell researchers are focused on a different method of creating pluripotent stem cells, called induced plu-ripotent stem cells, there may be some applications for SCNT-derived pluripotent cells are better suited.

Handling the reaction

The immunological reactions reported in the new paper will be a consideration if clinicians ever use SCNT-derived stem cells in human therapy, but such outcomes are far in the future, Weissman said. “This research informs us of the margin of safety that would be required if, in the distant future, we need to use SCNT to create pluripotent cells to treat someone,” Weissman said. “In that case we might be able to handle the immunological reaction using the immun engineering methods that are currently available.”

Currently, SCNT-derived cells are used in the im-mune reaction by using eggs from someone who is ge-netically similar to the recipient, such as a mother or sister, Schrepfer added.

The other Stanford co-author of the paper is Robert Robbins, MD, former professor of cardiothoracic surgery. Additional co-authors are from the University of Hamburg, Germany, the New York Stem Cell Foundation-Hamburg, the German Center for Cardiovas-cular Research, the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology and New York University in the United Kingdom.

The research was funded by the Else-Kröner-Fresenius Foundation, the Ludwig Institute for Stiftung Medicine.

The Stanford Department of Cardiothoracic Surgery also supported the work.

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