New version of antibiotic could eliminate risk of hearing loss

By Tracie White

On Christmas Eve, 2002, Bryce Faber was diagnosed with a deadly cancer called neuroblastoma. The 2-year-old’s treatment, which, in addition to surgery, included massive amounts of radiation followed by even more massive amounts of antibiotics, no doubt saved his life. But those same mega-doses of antibiotics, while staving off infections in his immunosuppressed body, instigated a permanent side effect: deafness.

“All I remember is coming out of treatment not being able to hear anything,” said Bryce, now a healthy 14-year-old living in Arizona. “I asked my mom, ‘Why have all the people stopped talking?’” He was 90 percent deaf.

“The loss has been devastating,” said his father, Bart Faber. “But not as devastating as losing him would have been.”

Treatment with aminoglycosides, the most commonly used class of antibiotics worldwide, is often a lifesaving necessity. But an estimated 20-60 percent of all patients who receive these antibiotics suffer partial or complete hearing loss.

Now, in a study published online Jan. 2 in the Journal of Clinical Investigation, researchers at the School of Medicine report that they have developed a modified version of an aminoglycoside that works effectively in mice without the risk of causing deafness or kidney damage, another common side effect.

The researchers hope to test versions of the modified antibiotic in humans as soon as possible.

“If we can eventually prevent people from going deaf from taking these antibiotics, in my mind, we will have been successful,” said Anthony Ricci, PhD, professor of otolaryngology-head and neck surgery and co-author of the study. “Our goal is to replace the existing aminoglycosides with ones that aren’t toxic.”

Four years in the making

It took the scientists four years of research to produce 5 grams of the newly patented antibiotic, N1MS, which is derived from sisorisporin.

Alan Cheng and Anthony Ricci are the senior authors of a study describing how they and fellow researchers modified a potent antibiotic, streptomycin, to eliminate its risk of causing deafness in mice.

Skin patch could help heal, prevent diabetic ulcers

By Sara Wykes

Researchers at the School of Medicine say they have developed a safe and effective skin patch to deliver a drug that enhances the healing of diabetes-related ulcers. The patch, which they tested in mice, may also serve as a way to prevent ulcer formation.

Among the more than 29 million people in the United States with either type 1 or type-2 diabetes, an estimated 15 percent develop ulcers. The ulcers, sores or open wounds that usually occur on the foot, become a secondary health condition that leads to prolonged disability, high rates of recurrence and increased mortality. Nonhealing wounds related to diabetes are the leading cause of nontraumatic amputations in the country.

What causes these ulcers has been known for several years. In 2009, researchers led by Geoffrey Gurtner, MD, a professor of surgery at Stanford, and a group of scientists at the Albert Einstein College of Medicine published a study pinpointing exactly how diabetes reduces the ability of tissue to form new blood vessels essential for wound healing. High levels of blood sugar compromise the body’s ability to grow the new blood vessels. That same study found a potential treatment: deferoxamine, or DFO, a drug already approved by the Food and Drug Administration to treat hemochromatosis, a condition in which too much iron accumulates in the body. DFO can correct the hematological problems associated with diabetes-related ulcers.

Nadeau’s team, which includes researchers in the chemical and biological sciences, pharmacology and medicine, as well as students in the graduate school, had made several discoveries that suggested DFO could correct the problems associated with diabetes-related ulcers.

In particular, in study published on line in December in the journal General Internal Medicine, the researchers showed that DFO enhances the healing of diabetes-related ulcers.

“Treatments for foot ulcers in diabetics have been ineffectual,” said Lloyd Minor, MD, dean of the School of Medicine. “Sean Parker’s generous gift will enable Stanford Medicine experts, under Dr. Nadeau’s leadership, to collaborate and innovate across academic disciplines for the benefit of millions of people with diabetes.”

“Sean is a lifelong friend of the School of Medicine, and a true champion of our research,” Minor said. “He is idealistic, ambitious and kind.”

“Looking across the landscape of diabetes treatment, what we are excited about is the idea of small molecules developed in the lab that go on to lead to drugs that are efficacious and can be delivered to patients who have been historically under-served,” Minor said. “It’s an integrated approach to diabetes treatment.”

“Why take this particular approach?” Minor asked. “It’s because with diabetes, there are many organisms for which you can develop new treatments.”

Researchers find evidence Medicare reforms have saved money, helped patients

By Becky Bach

Researchers have found evidence that Medicare reimbursement reforms can reduce the incidence of easily preventable, hospital-acquired health problems.

The reforms have worked as desired for at least two conditions, according to a study by researchers at the School of Medicine.

“We have a win-win,” said lead author Risha Gidwani, DrPH, a consulting assistant professor of medicine at Stanford and DrPH, a consulting assistant professor of public affairs health economics resource center in Menlo Park.

“The findings were published online Dec. 12 in the Journal of General Internal Medicine. In the past, the Centers for Medicare & Medicaid Services paid hospitals based on the treatment received, even though the treatment was needed for an easily preventable condition that the patient acquired in hospital.”

Silicon Valley entrepreneur and philanthropist Sean Parker announced Dec. 17 that he is donating $24 million to establish an allergy research center at the School of Medicine. The center will build on years of work by Stanford scientists to understand all types of allergies, which affect 30-40 percent of the global population.

Immunologist Kari Nadeau, MD, PhD, will lead the Sean N. Parker Center for Allergy Research at Stanford University. An associate professor of pediatrics, Nadeau will guide the center’s efforts to understand the underlying mechanisms of allergies in children and adults and to develop lasting allergy cures.

Nadeau has led the field in developing oral immunotherapy to combat severe food allergies, a treatment in which patients consume tiny but gradually increasing doses of their allergy triggers under a doctor’s supervision. The center’s researchers will continue to investigate food allergies, as well as to conduct studies of other allergenic conditions, such as drug allergies and reactions to environmental allergens. Parker, who co-founded the Internet file-sharing service Napster and served as the first president of Facebook, has a personal interest in the topic because of his own experience with severe food allergies.

“We are excited about the center because there is enormous clinical need for better understanding of and treatment for allergies,” said Lloyd Minor, MD, dean of the School of Medicine, in a press release announcing the donation. “For instance, the recent profound increase in the incidence of serious food allergy is fascinating and deeply concerning at the same time. Sean Parker’s generous gift will enable Stanford Medicine experts, under Dr. Nadeau’s leadership, to collaborate and innovate across academic disciplines for the benefit of millions of people with allergies.”

“I am thrilled and honored to direct the Sean N. Parker Center for Allergy Research at Stanford University,” Nadeau said in the release. “Sean is well-versed in immunology, and has been a fantastic partner to work with. He’s an entrepreneur and visionary, and we look forward to using this gift and center as the springboard to improve the lives of those adults with allergies through immunotherapy that goes beyond oral therapy.”

Napster co-founder gives $24 million to launch allergy research center

Alan Cheng and Anthony Ricci are the senior authors of a study describing how they and fellow researchers modified a potent antibiotic, streptomycin, to eliminate its risk of causing deafness in mice.

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See MEDICARE, page 6
A defect in communication between the two halves of the brain may be responsible for some cases of autism, according to a study by researchers at the School of Medicine.

They came to their conclusions by analyzing what’s called the human interactome — a vast network of interacting proteins — and by sequencing genomes and analyzing gene expression patterns in individuals with autism.

The study offers a possible explanation as to why the communication center of the brain, called the corpus callosum, is often abnormally small in people with the condition. Although most research has focused on neurons, this study also implicates the oligodendrocytes in the disorder. Oligodendrocytes coat the signaling arms of a neuron with an insulating substance called myelin, which enables electrical signals to move quickly from one neuron to another.

“Thus far, we have a glimpse of autism’s underlying biological framework, and it implicates a cell type and region of the brain that have not been extensively studied in this disease,” said Michael Snyder, PhD, professor and chair of genetics. “Until now, we’ve suspected that autism could be the result of defects in the neurons themselves. Now it appears that the oligodendrocytes can contribute to the problem by inhibiting nervous system signaling through poor cellular differentiation and myelination,” Snyder, who is also the Stanford W. Ascherman, MD, FACS, Professor in Genetics, is the senior author of the study, published online Dec. 30 in *Molecular Systems Biology*. The study was led by Stanley Ji Li, PhD, research assistant Minyi Shi and research associate Zhihai Ma share lead authorship of the study.

**Module 13**

The researchers didn’t directly analyze cellular functions in the corpus callosum. Instead, they layered many different types of previously published information about proteins in the brain onto a network that physiologically interacts with one another, those that are found in similar regions of the brain and those that work in the same pathway or physical process — with mutations found in people with autism. The overlap led them to a group of 119 proteins involved in how nerve cells communicate.

“This protein interaction module contained genes involved in the brain development and function of oligodendrocytes in the corpus callosum, which directly supports the idea that autism might be due to poor connectivity between brain hemispheres,” Li said.

The researchers first took the publicly available data about the human protein interactome and used it to identify which included information about more than 90,000 different proteins. They then used an algorithm to divide the interactome into 817 tightly associated subgroups of proteins. Members of these subgroups, or modules, were much more likely to physically interact with one another than with proteins outside their module.

Finally, they examined all the proteins of the 85 modules for overlap with any of the proteins encoded by 583 previously identified autism-associated genes and identified 85 in which many of the proteins were working together to accomplish specific biological tasks, such as adding a chemical tag to DNA-packaging proteins, or making proteins in a signaling cascade with phosphate molecules. One module, module 13, included many proteins involved in the process of synaptic transmission — the process by which neurons communicate with one another across gaps between cells.

Sequencing DNA

To confirm their findings, the researchers sequenced the complete genomes of 6 people with autism and the parents, or genomes, of an additional 19 individuals with the condition. The sequencing revealed 38 genes in module 13 that were significantly mutated. Twenty-one of these mutations had not been previously associated with autism, and 10 of the 28 had been shown in mice to affect behavioral traits or nervous system function.

The researchers consulted the Allen Human Brain Atlas, a kind of three-dimensional map of gene expression, to determine where the genes for the proteins in module 13 are expressed. Although half the genes are expressed throughout the brain, the other half are more specifically expressed in the corpus callosum. The co-expression of both halves of the module in the corpus callosum was further confirmed using frozen, postmortem brain samples, indicating it’s active in that region. Because oligodendrocytes are major cellular constituents of the corpus callosum, this study further implicated the involvement of module 13 in oligodendrocytes’ differentiation and myelination.

“Those findings tell us that we may have to focus our attention on genes involved in different cell types and brain regions, rather than those that had initially raised the suspicions of autism researchers,” Li said.

**Exciting advance**

Finding a new set of autism-associated genes is an exciting advance in the field of autism research, but it won’t necessarily lead immediately to new therapies for people with the condition, said Joachim Hallmayer, MD, an associate professor of psychiatry and behavioral sciences and a co-author of the study. “Autism is an extremely heterogeneous disease,” Hallmayer said. “Many genes have been implicated, but environment also plays a role. This study suggests a possible way to subtype patients into smaller, more homogeneous populations based on which genes are mutated. Some of these may be very easy to treat, based on their mechanism, whereas others may be much more difficult. For those in this category, it’s possible we could one day find a way to improve or correct the connection between the brain’s hemispheres.”

Other Stanford co-authors are assistant professor of psychiatry and behavioral sciences Alexander Urban, PhD, and pediatrician Jennifer Ziskin, MD, PhD; DNA sequencing program director Ghia Euskirchen; and life science research assistant Shuchun Zhao.

The research was funded by the National Institutes of Health and Stanford’s Department of Genetics also supported the work.
Scientists seek to map and treat the roots of mental illness

By Amy Adams

An interdisciplinary team of Stanford scientists is working to map the origins of mental illnesses in the brain and develop treatments to target those origins.

The collaboration could lead to improved treatments for depression, anxiety and post-traumatic stress disorder.

The researchers hope to noninvasively stimulate groups of neurons, or circuits, in the brain to identify those involved in mental disorders, as well as to treat the disorders.

Over the years, imaging technologies have revealed a lot about what’s happening in our brains, including which parts are active in people with depression, anxiety or post-traumatic stress disorder. But here’s the secret: Amit Etkin wants the world to know about those tautening images. They show the resulting brain state, not what is causing it.

This is important because until we know how circuits are causing these conditions — not just which are active later — scientists will never be able to treat them in a targeted way.

“You see things activated in brain images, but you can’t tell just by watching what is cause and what is effect,” said Etkin, MD, PhD, assistant professor of psychiatry and behavioral sciences. Etkin is co-leader of a new interdisciplinary initiative to understand which brain circuits underlie mental health conditions and find new ways to directly noninvasive treatments to those circuits.

“Right now, if a patient with a mental illness goes to see their doctor, they would likely be given a medication that goes all over the brain and body,” Etkin said.

“While medications can work well, they do so for only a portion of people and often only partially.”

Medications don’t specifically act on the brain circuits critically affected in that illness or individual.

Treating roots of mental illness

The new initiative, called NeuroCircuit, is part of Big Ideas in Neuroscience, an effort by the Stanford Neuroscience Institute to bring together teams of researchers from across disciplines to tackle ambitious projects in the brain field.

Stephen Baccus, PhD, an associate professor of neurobiology who co-leads the initiative with Etkin, said that what NeuroCircuit a big idea is the merging of teams trying to map circuits responsible for mental health conditions with teams developing new technologies to remotely access those circuits.

“Many psychiatric disorders, especially disorders of mood, anxiety and post-traumatic stress disorder, involve malfunction within specific brain circuits that regulate emotion and motivation, yet our current pharmacological treatments affect circuits all over the brain,” said institute director William Newsome, PhD, professor of neurobiology.

“Understanding psychiatric disorders holistically means treatments that target specific circuits that are involved in disorders,” Baccus added.

“The connection between the people who develop the technology and carry out research with the clinical goal, that’s what’s really come out of the Big Ideas.”

Brain control

Etkin has been working with a technology called transcranial magnetic stimulation, or TMS, to map and remotely stimulate parts of the brain.

The device, which looks like a pair of doughnuts on a stick, generates a strong magnetic current that stimulates circuits near the surface of the brain.

TMS is currently used as a way of treating depression and anxiety, but Etkin said the brain regions being targeted are the ones available to TMS, not necessarily the ones most likely underlying a person’s condition.

Pairing TMS with another technology that shows which brain regions are active, Etkin and his team can stimulate one part of the brain with TMS and look for a reaction elsewhere. These studies can eventually map the relationships between brain circuits and identify the circuits that underlie mental health conditions.

The team also is working to improve TMS to make it more useful as a therapy. TMS currently only reaches the surface of the brain and is not very focused.

The goal is to improve the technology so that it can reach structures deeper in the brain in a more targeted way. “Right now they aren’t specifically acting on the brain circuits,” Baccus said.

“Many years scientists have learned that at the microscopic level that’s the merging of teams trying to map circuits near the surface of the brain to identify the circuits that underlie mental health conditions,” Baccus said.

Leaders of the team have been working together for about five years, and in 2012 got funding from Bio-X NeuRoVentures, which eventually gave rise to the Stanford Neurosciences Institute, to partner on this work. Before merging with Etkin’s team, his lab had been focusing on the technology without specific brain diseases in mind.

“Those really gives a target and a focus to the technology,” he said.

“Gary has made a significant impact on neonatal health worldwide, particularly by championing the use of chlorhexidine for umbilical cord cleansing, and by developing community-based guidelines for the essentials of newborn care,” said Michele Barry, MD, professor of medicine and director of Stanford’s Center for Innovation in Global Health. “We are so glad to have him join us.”

In his new role, Darmstadt will collaborate with several other Stanford experts in international medicine, including Barry and Yvonne Maldonado, MD, professor of pediatrics and of health research and policy.

He plans to study how to reduce gender inequality in developing countries in order to improve community health. Darmstadt will also examine ways of ensuring healthy birth, growth and development of children in these countries. “As child survival rates improve, we need to focus more on optimizing the neurodevelopment and productivity of children so that they have opportunities to grow up and develop to their full potential,” he said.

Within the Department of Pediatrics, Darmstadt will work in the Division of Neonatal and Developmental Medicine and the Division of Infectious Diseases. He will also be an associate dean for maternal and child health, reporting to Stevenson, and will co-direct the Department of Pediatrics’ Global Health Initiative.
Expert pilots process multiple visual cues more efficiently

By Bjorn Carey

Landing an airplane is one of the most difficult piloting techniques to master, and the danger increases when 80 percent of all airplane accidents and 25 percent of fatalities occur during the final approach and landing.

New research by scientists at the School of Medicine and the VA Palo Alto Health Care System reveals that expert pilots make better decisions during this phase than less experienced pilots because their brains behave more efficiently.

The study, published Nov. 26 in *PLOS ONE*, could lead to technology and training that aid less efficient brain behaviors in order to improve flight safety.

The researchers rigged a fMRI machine so that 20 pilots—12 moderately experienced pilots and eight experienced pilots—could operate the controls of a flight simulator while having their brain activity scanned in real time. The simulator mimicked the cockpit of a single-engine airplane, and the pilots were instructed to land at a virtual San Francisco International Airport.

The trial started at 350 feet of altitude. They were instructed to begin their descent based only on their instruments as they would normally do in real life. From there, they were given a series of instructions: land at a virtual San Francisco International Airport.

The pilots would then need to flash their gaze from the instruments to the runway and back to make a snap decision about whether to land, and train them to reallocate resources in the brain more efficiently,” said Adamson. “If we are able to train pilots to process instruments and other visual cues more efficiently, you could reduce the likelihood of accidents during landing.”

Although these findings were obtained by testing aircraft pilots, they may also have implications for skilled task performance and aging in general. Prior research has shown slower speed of information processing predicts worse performance on aviation-related tasks in older pilots. The current research offers an insight into how more efficient brain activity and information processing may provide a countermeasure to loss of speed of processing with aging.

The study’s senior author is Jerome Yeraguge, MD, professor of psychiatry and behavioral sciences, associate chief of staff for mental health at the Palo Alto VA and director of the Stanford/VA Aging Clinical Research Center. Other co-authors are Joy Taylor, PhD, a clinical associate professor of psychiatry and behavioral sciences at Stanford and assistant director of the Aging Clinical Research Center; Daniel Heralder, a former research assistant at the medical school; and Adamson added.

Better decisions, half the brain activity

After multiple attempts per pilot, the results showed that the expert pilots made the correct decision about whether to make a landing attempt or abort 80 percent of the time, whereas the moderately experienced pilots did so only 64 percent of the time. Interestingly, the fMRI scans revealed that the expert pilots scored higher while displaying only half as much brain activity.

Landing a plane involves constantly scanning instruments as well as the view out the windows, said Maheen Adamson, PhD, lead author of the study and a clinical associate professor of psychiatry and behavioral sciences at Stanford. Reduced neural activity in expert pilots indicates that they are able to complete the task at hand with fewer brain resources. She suspects that the brain’s ability to streamline multiple visual inputs is the result of experience.

This is an area of the brain involved in regulating gaze as the eyes quickly shift their focus to different fixed objects. The work needs to be replicated to confirm the caudate nucleus’ role in instrument scanning, Adamson added.

Other brain structures or mechanisms might be playing a role in visual processing for pilots. But this work opens the door to pairing fMRI and flight simulators. The researchers might also be able to design interactive lessons that guide expert pilots into behaviors that mimic the more efficient brain activity of expert pilots.

Other implications

“In the future, we could put a trainee in a scanner and see what mechanism in their brain they’re using to get better at the task, and train them to reallocate resources in the brain more efficiently,” Adamson said. “If we are able to train pilots to process instruments and other visual cues more efficiently, you could reduce the likelihood of accidents during landing.”

“The data show that this abnormal change in stem cells could be inhibited in laboratory mice by giving the animals a drug that is already approved for use in humans. The drug works by blocking a signaling pathway involved in the development of fibrosis. Although much more research is needed, the scientists are hopeful that a similar approach may be one day work in children with muscular dystrophy.”

“This is an area of the brain involved in regulating gaze as the eyes quickly shift their focus to different fixed objects.”

Researchers rigged a fMRI machine so that 20 pilots—12 moderately experienced pilots and eight experienced pilots—could operate the controls of a flight simulator while having their brain activity scanned in real time. The flight simulator depicted either a relatively clear view of the runway (top) or conditions that made it too foggy to land (bottom).

Stem cells faulty in Duchenne muscular dystrophy, researchers find

By Krista Conger

Like human patients, mice with a form of Duchenne muscular dystrophy undergo progressive muscle degeneration and accumulate connective tissue as they age. Now, researchers at the School of Medicine have found that the fault may lie partly in the stem cells that surround the muscle fibers.

They found that during the course of the disease, the stem cells become less able to make new muscle and instead begin to express genes involved in the formation of connective tissue. Excess connective tissue—a condition called fibrosis—can accumulate in many organs, including the lungs, liver and heart, in many different disorders. In the skeletal muscles of people with muscular dystrophy, the fibrotic tissue impairs the function of the muscle fibers and leads to increasing weakness and stiffness, which are hallmark signs of the disease.

The researchers discovered that this abnormal change in stem cells could be inhibited in laboratory mice by giving the animals a drug that is already approved for use in humans. The drug works by blocking a signaling pathway involved in the development of fibrosis. Although much more research is needed, the scientists are hopeful that a similar approach may one day work in children with muscular dystrophy.

“This cells are losing their ability to produce muscle, and are beginning to look more like fibroblasts, which secrete connective tissue,” said Thomas Rando, MD, PhD, professor of neurology and neuroscientific. “It’s possible that if we could prevent this transition in the muscle stem cells, we could slow or ameliorate the fibrosis seen in muscular dystrophy in humans.”

A paper describing the researchers’ findings was published Dec. 17 in *Science Translational Medicine*. Rando, the paper’s senior author, is director of the Glenn Laboratories for the Biology of Aging and founding director of the Muscular Dystrophy Association Clinic at Stanford. Former postdoctoral scholar Stefano Biressi, PhD, is the lead author. Biressi is now at the Centre for Integrative Biology at the University of Trento in Italy.

Duchenne muscular dystrophy is a devastating disease that affects about 1 in every 5,600 boys born in the United States. Patients usually experience severe, progressive muscle weakness that confines them to a wheelchair in early adolescence and eventually leads to paralysis. It’s caused by mutations in the dystrophin gene, which encodes the dystrophin protein. The dystrophin protein serves to connect muscle fibers to the surrounding external matrix. This connection stabilizes the fibers, enhancing their strength and preventing injury. Sufferers are nearly always boys because the dystrophin gene is located on the X chromosome.

Under normal conditions, muscle stem cells respond to muscle damage by dividing into two daughter cells, one of which becomes new muscle, while the other remains a stem cell. However, in the mice miss- ing the dystrophin gene, the muscle stem cells slowly assume a different fate. They begin to resemble fibroblasts instead of muscle-making machines.
Blocking receptor in immune cells counters ‘Alzheimer’s’ in mice

By Bruce Goldman

The mass die-off of nerve cells in the brains of people with Alzheimer’s disease may ultimately arise from a common mechanism that is different in different brain classes, called microglia, begin to fall down on the job, according to new findings by researchers at the School of Medicine.

The researchers found that, in mice, blocking the action of a single molecule on the surface of microglia restored the cells’ ability to get the job done — and reversed memory loss and myriad other Alzheimer’s-like symptoms.

The study, published online Dec. 8 in The Journal of Clinical Investigation, illuminated the importance of microglia and could lead to new ways of warding off the onset of Alzheimer’s disease, which is predicted to afflict 15 million people by mid-century unless some form of cure or prevention is found. The study also may help explain an intriguing association between aspirin and reduced rates of Alzheimer’s.

Microglia, which constitute about 10-15 percent of all the cells in the brain, actually resemble immune cells considerably more than they do nerve cells. “It’s like a half-way point between a neuron and a macrophage,” said Katrin Andreasson, MD, professor of neurology and neuroscientific and the study’s senior author. “Our experience has been that microglia look like gravestones on the right track counter memory loss and preserves healthy brain physiology.

Implicated: a single molecule

A microglial cell serves as a front-line sentry, monitoring its surroundings for suspicious activities and materials by probing its local environment. If it spots trouble, it releases substances that recruit other immune cells to the scene, said Andreasson. Microglia are tough cops, protecting the brain against invading bacteria and viruses by gobbling them up. They are adept at calming things down, too, clamping down on inflammation if it gets out of hand. They also work as garbage collectors, chewing up dead cells and molecular debris strewn among living cells, including clusters of a protein called A-beta, notorious for aggregating into gummy deposits called Alzheimer’s plaques, the disease’s hallmark.

A-beta, produced throughout the body, is as natural as it is ubiquitous. They also reduce the production of recruiting chemicals and not macrophages, which are responsible for that inflammatory activity, whether nerve cells or microglia were responsible for that inflammatory activity, or what its precise consequences were. So they determined to find out.

Preserving memory

The experiments began in a dish, isolating viable microglia from the brain. It’s relatively easy to harvest large numbers of their close cousins, immune cells called macrophages. These cells circulate throughout the body and are abundant in engineered cell samples. While not carbon copies of one another, microglia and macrophages share similar histochemical, biochemical and behavioral features.

When placed in a dish with soluble A-beta clusters, macrophages drawn from young mice responded calmly, producing recruiting chemicals and not macrophages, the output of A-beta-cheming enzymes in these young cells was robust. But macrophages from aged rats, which had differing A-beta’s presence incur a big increase in EP2 activity in these cells, resulting in aayed-up output of inflammatory molecules and reduced generation of recruiting chemistries and A-beta-digesting enzymes.

This early hint that age-related changes in EP2 action in microglia might be promoting some of the neuropathological features implicated in Alzheimer’s was borne out in subsequent experiments for which Andreasson’s team used mice genetically predisposed to get the mouse equivalent of Alzheimer’s, as well as other-wise normal mice into whose brains the scientists injected either A-beta or a control solution. In both groups of mice, the expected deleterious effects on memory and learning didn’t arise if EP2 within microglial cells was absent, as a result of a genetic manipulation. Blocking microglial EP2 activity significantly improved these animals’ performance on two kinds of standard memory tests: one that assesses how quickly a mouse forgets that it has encountered an object before, and another that rates the mouse’s ability to remember where a particular object was located.

Looking beyond aspirins

Clearly, knocking out EP2 action in A-beta-provoked microglia benefited memory in mice that had either gradually (the ‘Alzheimer’s’ mice) or suddenly (the brain-injected mice) acquired excessive A-beta in their brains. Likewise, mouse microglia bioengineered to lack EP2 vastly outperformed unaltered microglia, in A-beta-challenged brains, at such critical tasks as secreting recruiting chemicals and factors beneficial to nerve cells and in producing inflammation-countering, rather than inflammation-spurring, proteins.

Yet, epidemiological reports suggest that the use of nonsteroidal anti-inflammatory drugs, such as aspirin, can prevent the onset of Alzheimer’s — although only if their use is initiated well before any signs of the disorder begin to show up in older people, Andreasson said. “Once you have any whim of memory loss, these drugs have no effect,” she said.

NSAIDs mainly act by blocking cyclooxygenase (COX-1 and COX-2); these enzymes create a molecule that can be converted to several different substances, including PGE2, a hormone-like chemical that triggers EP2 action.

Although PGE2 is known to regulate inflammatory changes in the brain, it exercises diverse, useful functions in different tissues throughout the body, from influencing blood pressure to inducing labor. Complicating matters, PGE2 is just one of five prostaglandins origi-nating from the precursor molecule produced by COX-1 and COX-2. So aspirin and other COX-1 and COX-2-inhibiting drugs may have myriad effects, not all of them beneficial. It may turn out that a compound blocking only EP2 action on microglial cells, or some downstream conse-quences within microglial cells, would be best-suited for fending off Alzheimer’s without side effects, said Andreasson. Meanwhile, her group is exploring the biological mechanisms via which PGE2 signaling pushes microglia over to the dark side.

Dystrophy

Bretski and Rando used a strain of laboratory mice in which the muscle stem cells were engineered to glow with a fluorescent light when treated with a drug called tamoxifen. They then bred the mice with another strain in which the dystrophin gene is mutated, called tamoxifen. They then bred the mice with an-transfected microglia restored the cell’s ability to get the job done — and reversed memory loss and myriad other Alzheimer’s-like symptoms. For this reason, the researchers took the expression of myostatin, a protein that regulates muscle mass, and the regeneration of muscle in response to injury, was nearly completely lacking in many of the muscle stem cells in these mice. Over 1 month, the expression of fibrotic genes increased compared with that of control animals. The cells from the dystrophic animals also showed less muscle-nerthing next to the muscle fibers, they had begun to move away into the spaces between tissues.

The role of a signaling pathway

Rando and Bretski knew that a similar, but much less pronounced, accumulation of connective tissue in muscle fibers occurs during normal aging. That process is governed by signaling proteins, which include the Wnt and TGF-beta protein families. Wnt plays a critical role in embryonic development and cancer; TGF-beta controls the proliferation and migration of different cell types, said Rando. They wondered whether blocking the Wnt/TGF-beta pathway in the dystrophic mouse would inhibit fibrosis in the animals’ muscles.

The researchers turned to a drug called losartan, which is used to treat high blood pressure. Losartan inhibits the expression of the genes for TGF-beta type 2, and 2. The researchers thought it would probably interrupt the signaling pathway that leads the muscle stem cells astray. But when they treated mice with losartan, they found, did in fact prevent the muscle stem cells from expressing fibrosis-associated genes and partially maintained muscle function.

“This scar tissue, or fibrosis, leaves the muscle less elastic and impairs muscle function,” Rando said. “And it’s quite possible that fibrosis is important in maintaining normal muscle function, things get out of control.”

Next steps

Because TGF-beta type 1 plays many roles throughout the body, the researchers are now working including PGE2, which is involved in the transition of the muscle stem cells. They’re also interested in learning how to translate these findings to other diseases.

Fibrosis seems to occur in a vicious cycle,” Rando said. “As the muscle stem cells become less able to regenerate new muscle, the tissue is less able to repair itself after damage. This leads to fibrosis, which then further impairs muscle formation. Understanding the biological basis of fibrosis could have a profound effect on many other diseases.

Other Stanford researchers include visiting scholar Elen Miyabara, PhD, from the University of São Paulo, Brazil; postdoctoral scholars Kunpeng Cheng, PhD, and Zhen Lian, MD, PhD; life-sciences research assistants Qian Wang and Maharsi Panchar and graduate student Taylor Loz. The study was supported by the National Institutes of Health, the Alzheim-er’s Association, the Swedish Re-search Council and the National Science Foundation. Stanford’s Department of Neurology and Neurological Sciences also supported the work.

Katrín Andreasson is senior author of a study that implicates malfunction in the brain’s immune cells in Alzheimer’s disease.
Penetrate the outermost layer of the skin. The researchers decided to investigate an alternative: local delivery of just enough medication directly to an ulcer through a patch applied to the skin.

Dominik Duscher, MD, a postdoctoral scholar in surgery, and Ergenios Neafses, MD, an instructor at the Stanford Cardiovascular Institute, share lead authorship of a paper describing the findings of the new study. Gurtner is the senior author. The paper was published online Dec. 22 in the Proceedings of the National Academy of Sciences.

Challenges of developing a patch

Developing the skin patch raised a set of formidable challenges, which the Stanford team took on, step by step, working with materials engineers led by co-author Jayalakshmi Rajadas, PhD, director of Stanford’s Biomaterials and Advanced Drug Delivery Laboratory.

The goal was needed to be modified to penetrate the outermost layer of the skin to activate the formation of new blood vessels, but its release also needed to be controlled to prolong the availability of the DFO at a therapeutic level. It took nearly four years of attempts before the team produced a solution: Envelope the DFO with a surfactant, which would lower the DFO’s natural surface tension and transform its molecules into microparticles that could penetrate the skin, then embed them in a pliable polymer matrix, a couple of millimeters thick, that would protect the fragile DFO microparticles and disperse them gradually as the matrix disintegrated.

“The mice tolerated it very well,” Duscher said, which could bode well for humans. One of the biggest challenges is applied — the moisture in skin makes a natural barrier that supports new vascular growth.

‘Hope to start clinical trials soon’

Not only did the wounds in the mice heal more quickly, Duscher said, but the quality of the new skin was even better than the original. The researchers also used the DFO matrix on a mouse with diabetes to see if it would prevent ulcer formation — and it did. “We were very excited by the results,” Duscher said, “and we hope to start clinical trials soon to test this in humans.”

“This same technology is also effective in preventing pressure ulcers, which are a major source of morbidity and mortality in patients with neurologic injury or the elderly,” said Gurtner, who is also the Johnson & Johnson Distinguished Professor in Surgery II. “The actor Christopher Reeve actually died from a pressure ulcer and not his spinal cord injury, which really emphasizes the extremely limited therapeutic options for these patients.”

Other Stanford co-authors of the paper are postdoctoral scholars Michal Januszyk, MD, Melanie Rodrigues, PhD, and Zeebaa Maan, MBBS, MS, MRCS; former visiting medical student Robert Renner; Mohammed Inayathali-

LS, PhD; basic life sciences research associ-

ees; lab manager Arthea Whitmore; graduate student Graham Walmsey; re-

dent Michael Galvez, MD; life sciences research assistant Alexander Whittham; and research scientist Andrey Malkovsk-

yi, PhD.

The research was funded by National Institutes of Health, the Harrington Dis-

cove Foundation, the Hapgy Family En-

dowed Fund in Stem Cell Research and Regenerative Medicine, and The Oak Foundation. Stanford’s Department of Surgery also supported the work. SW

Sara Wykes is a writer for Stanford Health Care’s communications office.

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the hospital. But in 2008, CMS stopped paying for the additional costs of treating nine preventable, hospital-acquired conditions.

Clots and blockages

Gidwani selected two of these conditions: pulmonary embolism, a blockage of an artery that supplies the lung; and deep-vein thrombosis, a blood clot that forms in a vein that can cause pulmonary embolism. Patients who receive hip or knee replacements are likely to develop these conditions without proper care, which usually consists of ambulation, mechanically-assisted movement or medication.

She examined records from 2007 to 2009 from a national database of American hospital discharges, compar-

ing Medicare patients ages 65-69 who received a hip or knee replacement with non-Medicare patients ages 60-64 who received the same procedures.

When CMS stopped paying for treating deep-vein thromboses and pulmonary embolisms, the incidence of these conditions after hip or knee replacement sur-

gery dropped 35 percent in the Medicare population, Gidwani said.

In the younger, non-Medicare population, the in-

cidence of these two conditions increased, although they also decreased in the patients over age 65 who had private insurers. There are more than 1 million hip or knee replacements performed in the United States each year, and over 60 percent of them are paid for by Medicare.

Gidwani ran statistical analyses to ensure the results were not due to differences in the length of hospital stay or potential differences in billing practices among the hospitals.

Getting results

“This study provides evidence the reimbursement reform had the desired effect,” Gidwani said. “This is important information if Medicare or private payers are thinking about expanding value-based purchasing programs.”

The co-author is Jay Bhattacharya, MD, PhD, pro-

fessor of medicine and director of the Stanford Program on Medical Outcomes. “It may seem obvious that Medicare should use pay-
m ent incentives for providers to encourage better and more appropriate care for patients, but there is always a risk of unintended consequences when Medicare cuts payments for services,” Bhattacharya said. “In this case, we have found evidence that Medicare’s refusal to pay for complications arising from hip and knee surgery really did reduce the incidence of those complications. This has many more opportunities to improve patient outcomes by reforming provider payment practices, though lots of careful research will be needed to identify them.”

Stanford’s Department of Medicine helped to support the study, for which there was no outside funding.

Lecture series established by dean kicks off Jan. 23; initial talks to focus on diversity

Lloyd Minor, MD, dean of the School of Medicine, has established the Dean’s Lecture Series to bring leading innovators from a variety of fields to Stanford.

Initially, the series will focus on diversity, kicking off Jan. 23 with a presentation by Rosalind Hudnell, the chief diversity officer at Intel.

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nor said. “It is an integral part of what it means to lead the biomed-
ic research at Stanford. Helen Koo, PhD, co-founder of the Center for Pulmonary Vascular Disease.

The following lectures have been scheduled:

• Jan. 23: Hudnell, chief diver-

sity officer and general director of education and external relations at Intel.

• Feb. 20: Vivek Wadhwa, fellow at the Center for Corporate Gover-

nance at Stanford.

• May 1: Ruth Simmons, presi-

dent emerita of Brown University. All lectures will be held from noon to 1 p.m. in Berg Hall at the Ka Shing Center for Learning and Knowledge.

For more information on the lecture series, visit http://med.stan-

ford.edu/deanslectures.

Pulmonary hypertension program accredited as comprehensive care center

The Stanford Adult Pulmonary Hypertension Program is one of only seven programs nationwide to have been accredited as a comprehensive care center by the Pulmonary Hypertension Association.

“We’re excited to be one of the first centers in the country to get this accreditation,” said Juliana Liu, a nurse practitioner in the Vera Moulton Wall Center for Pulmonary Vascular Disease. “It’s really a recognition for the work we’ve been trying to do for many years.”

Pulmonary hypertension, high blood pressure in the arteries and capil-
laries of the lungs, can lead to right-

heart failure, its causes may include genetic, environmental and immuno-

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mician, a type of aminoglycoside. N1MS cured urinary tract infection in mice just as well as gentamicin, but it doesn’t cause deafness, study results show. The study presents a promising new approach to generating a new class of novel, nontoxic antibiotics. The two senior authors — Ricci and Alan Cheng, MD, associate professor of otorhinolaryngology-head and neck surgery — inherited forces in 2007 to explore the idea of creating new and improved versions of aminoglycosides based on a simple yet groundbreaking idea born of Ricci’s basic science research into the biophysics of how hearing works within the inner ear. “It’s a nice example of how basic science research is directly translatable into clinical applications,” said Ricci.

Ricci is an expert on the process by which sound waves open ion channels within the sensory hair cells of the inner ear, allowing their conversion to electrical signals that eventually reach the brain. Because aminoglycosides cause deafness by killing these nonregenerating hair cells, Ricci postulated, why not simply make the drug molecules unable to enter the cells’ channels? The idea made sense to Cheng. “As a clinician-scientist, I treat kids with hearing loss,” Cheng said. “When a drug causes hearing loss, it is devastating, and it’s especially disturbing when this happens to a young child as they rely on hearing to acquire speech.”

“When I came to Stanford seven years ago from the University of Washington, I was exploring the angle that maybe we could add drugs to protect the ear from toxicity. Tony brought up this new idea: Why don’t we just let the drug get in? Great idea, I thought. When we do that, it works.”

A potent antibiotic

For 20 years, and despite newer, alternative antibiotics, aminoglycosides have remained the mainstay treatment worldwide for many bacterial diseases, including pneumonia, meningitis, and sepsis. They also are used when other antibiotics have failed to treat infections of unknown origins. The drug’s popularity is also in part, to their low cost, lack of need for refrigeration and effectiveness at treating bacterial infections at a time when the declining potency of antibiotics is a major public health concern.

They are frequently used in neonatal intensive care units to battle infections, or even the threat of infection in premature babies. Exactly how many premature babies suffer hearing loss as a side effect of treatment with the drug is unknown, Ricci said.

“The toxicity of these drugs is something we accept as a necessity evil,” said Datta Mochly-Rosen, PhD, director of SPARK at Stanford that assists scientists in moving their discoveries from bench to bedside. “It’s a nice example of how basic science research can provide a project that could make a huge difference in human health.”

For decades, researchers have looked for ways of preventing aminoglycosides from killing off the hearing cells of the inner ear, Ricci said.

“So many approaches have failed,” Ricci said. “The main problem has been that if you succeeded in stopping the drug from killing hair cells, then you also stopped its antimicrobial effect. The drug just doesn’t work anymore.”

The goal, Ricci said, was to keep the antibacterial properties of the drug intact while preventing it from entering the inner ear's ion channels. He and his fellow researchers used data from structural biologists at Stanford who better understood how the antibiotics reduce toxicity to the ear while retaining antimicrobial action.

Greenhouse, for example, researchers made nine different compounds derived from sisomicin. All nine were significantly less toxic than sisomicin to hair cells when tested in the lab. They then looked for compounds that were toxic to the kidneys. These were not delivered to the mice.

“[When a drug] causes hearing loss, it is devastating.”

Poor semen quality linked to hypertension, other health problems: new study finds

By Bruce Goldman

A study of more than 9,000 men with fertility problems has found an association between the number of different defects in a man's semen and the likelihood that the man has other health problems. The study, conducted by investiga-

tors at the School of Medicine, also links poor semen quality to a higher chance of having various specific health conditions, such as hypertension, and more generally to skin and endocrine disorders.

The findings, published online Dec. 10 in Fertility and Sterility, may spur more comprehensive approaches to treating men's infertility. The results, the authors said, are to the knowledge of performing complete physical examinations of men experiencing reproductive difficulties.

“Fertility problems affect 15 percent of all couples have fertility issues, and in half of those cases the male partner has semen deficiencies,” said study senior author Michael Eisenberg, MD, assistant professor of urology and director of male reproductive medicine at Stanford Hospital and Surgery at Stanford.

“We should be paying more attention to these millions of men. infertility is a warning. Problems with reproduction may be showing the association between semen quality and overall health,” said study co-author Kayvon Sotoudeh, MD. A study Eisenberg co-authored a few years ago showed that infertile men had higher rates of overall mortality, as well as mortality linked to heart problems, in the years following an infertility evaluation.

“Because we’re already spotting signs of trouble in young men in their 30s,” he said.

Analyzing medical records

In the new study, Eisenberg and his colleagues analyzed the medical records of 9,387 men, mostly between 30 and 50 years old, who had been evaluated at Stanford Hospital & Clinics (now Stanford Health Care) between 1994 and 2011, to determine the cause of their infertility. The men had routinely provided semen samples, which the researchers assessed for sperm parameters, including volume, concentration and motility. In about half of all the male infertility cases, the problem was abnormal semen; in the rest, the fault lay elsewhere.

So, using the database, the investigators were able to identify a group of men who had semen defects to that of the men who didn’t.

With a median age of 38, this was a fairly young group. And, a large percent of all the men had some addi-

tional health problem besides the fertility problem. The study revealed that 15 percent of all genes in the human genome are connected fairly directly to reproduction, and most of these genes also have diverse functions in other bodily systems. He also noted that it may not be a disease itself, but the treatment for the disease, that actually responsible for reproductive malfunction. He said it is preventing this particular problem.

“A man’s health is strongly correlated with his semen quality,” he said. “Given how much it affects a man’s overall health, the study of the disease, the men, in particular, may help improve the health of both babies and mothers.”

“Many for families, a baby’s NICU stay is like a roller coaster ride, with ups and downs, triumphs and setbacks,” said Jennifer House, PhD, the March of Dimes president. “The March of Dimes developed the NICU Family Support Program to support families during their baby’s time in the NICU and help them be involved in their baby’s care.”

Gynna Cano, whose baby Maximus spent six weeks at Lucile Packard Children’s Hospital Stanford after he arrived 8 weeks early last summer, was one of the first parents to receive materials from the new program.

“There’s a lot of information, and it was very helpful,” said Cano, who brought her baby home in late August. “I had lots of questions and concerns taking him home from the hospital, so it helped to ease the care we received.”

Diana Webb is a freelance writer.

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of Dimes NICU Family Support Program is available in communities across the country and serves 90,000 families each year. At Lucile Packard Children’s Hospital Stanford, it’s part of a longstanding collaboration with the nonprofit to improve the health of both babies and mothers.

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Give saved for life!
Sleep center director adopts a narcoleptic canine companion

When Bear, the last member of Stanford’s colony of narcoleptic dogs, died last year, Emmanuel Mignot, MD, PhD, professor of psychiatry and behavioral sciences, thought he was done keeping dogs with the chronic brain disorder. At least for a while.

But soon after Bear’s death, Mignot’s phone rang: A dog breeder in the Northeast had a Chihuahua puppy that collapsed to the ground when he got excited. Did Mignot want him?

Bear had left a big hole in his heart, and in the home he shared with his wife, Servane Briand. But he felt he was ready for a dog again, although he had previously discovered a gene that triggers narcolepsy in some dogs, his research direction had shifted: He was trying to document the links between the immune system and narcolepsy in humans. Briand, too, was reluctant to adopt a new dog.

But the dog needed a home, and Mignot, who directs the Stanford Center for Sleep Sciences and Medicine, asked himself, who better than an expert on canine narcolepsy to care for the animal?

He flew to Vermont last spring and, once he met the wriggly, black-and-white puppy with a few brown splotches, the decision was made.

Now Watson — named after the character in Sherlock Holmes fiction, the IBM computer sentient and the famed geneticist — is in California, devoting his paws to a pup he who just happens to fall asleep when he gets excited.

Although Watson is a bit shy around newcomers, Mignot takes him into the clinic when he treats children with narcolepsy, a growing population that can experience severe symptoms such as almost constant sleepiness and sudden episodes of muscle paralysis that occur with laughter.

Mignot can trigger one of Watson’s cataplexies by proffering certain foods, especially Whole Foods oat roast beef, or playing with the dog. Bending down, cooing to Watson in French, Mignot (a native of France) got ready to give the dog a piece of pork. Watson took a big sniff and staggered backwards, struggling to ward off the attack that was paralyzing his muscles — pushing him toward sleep in just seconds. He lay still, just trembling to his feet and lunging for the food.

Sometimes Watson’s attacks are quick, other times they occur repetitively, Mignot said. His former narcoleptic dog, Bear, predictably had sleep attacks when he saw any kind of new food, even broccli, but Watson is a bit more variable, suffering attacks when Mignot arrives home from work or when he spots a favorite toy, Mignot said.

Watson’s entertaining performance can calm frightened children and help them understand their condition, Mignot said.

In humans, narcolepsy is caused when the immune system attacks certain neurons in the brain. These neurons produce a peptide called hypocretin that promotes wakefulness and inhibits dreaming. Some dogs have that type of narcolepsy as well, although others have a genetic form that stems from a mutation in the hypocretin receptor gene. Watson is a family pet and has not undergone any kind of genetic testing, so Mignot doesn’t know what type of narcolepsy he has.

The Stanford narcoleptic dog colony, started by William Dement, MD, PhD, professor of psychiatry and behavioral sciences, allowed Mignot to discover the genetic basis for canine narcolepsy and enhanced understanding of the human condition, which affects about 1 in 2,000 people.