Brain cells that cause pain aversion found

By Hanae Armitage

If you step on a tack, neurons in your brain will register two things: that there’s a piercing, physical sensation in your foot, and that it’s not pleasant. Now, a team of scientists at Stanford has identified a bundle of brain cells in mice responsible for the latter — that is, the negative emotions of pain.

Pain research has traditionally focused on the neurons and molecules at the forefront of pain perception — the cells in nerves that process stings, cuts, burns and the like — and ultimately convey a physical threat message. What Grégory Scherrer, PhD, assistant professor of anesthesiology and of neurosurgery, and Mark Schnitzer, PhD, associate professor of biology and of applied physics, are studying goes one step further. “We’re looking at what the brain makes of that information,” Scherrer said. “While painful stimuli are detected by nerves, this information doesn’t mean anything emotionally until it reaches the brain, so we set out to find the cells in the brain that are behind the unpleasantness of pain.”

Peeping at pain neurons

Backed by animal-brain imaging and molecular testing, the researchers have found an ensemble of cells in the amygdala, a region of the brain classically associated with emotion and fear, that seems to specifically function as an on-off switch for pain aversion. And although the finding was made in mice, there’s reason to think it could one day serve as a therapeutic target for human pain, since the mouse and human amygdala aren’t so different in function. Researching this group of cells could reveal a potential treatment for chronic pain, the scientists hope.

The idea is that patients suffer from a binary emotional response to pain: they either feel emotional until it reaches the brain, or even help prevent that damage.

The difference, Woo said, may be that this second group of patients has collateral arteries, tiny arteries that bypass blockages in hearts’ major arteries and feed areas of the heart starved of oxygen. “They are like the side streets that let you get around a traffic jam on the freeway,” Woo said. Such collateral arteries could help people with other conditions, people recovering from a heart attack, except that collateral arteries are only seen in a minority of patients.

Now Woo, Red-Horse and their colleagues have discovered how these collateral arteries are formed and a signaling molecule that promotes their growth in adult mice, offering hope that collateral arteries may be coaxed to grow in human patients.

Their findings were published Jan. 24 in Cell. Red-Horse, a member of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, and Woo, a member of the Stanford Cardiovascular Institute, share senior authorship of the paper. Postdoctoral scholars Soumyadeep Das, PhD, and Andrew Goldstone, MD, PhD, are co-lead authors.

Scientists find protein promotes small artery growth to damaged heart tissue in mice

By Christopher Vaughan

A collaboration between basic and clinical scientists at Stanford has revealed a protein that promotes the growth of small arteries into oxygen-starved heart tissues in mice.

Kristy Red-Horse, PhD, associate professor of biology, and Joseph Woo, MD, professor of cardiothoracic surgery, think the growth of these new arteries may help heal damage caused by heart disease or heart attack, or even prevent that damage.

In clinical practice, Woo has observed that patients with blockages in major arteries feeding the heart often have confoundingly different outcomes. “Some patients have a blockage in one coronary artery and die; other patients have multiple blockages in multiple areas but can run marathons,” said Woo, who holds the Norman E. Shumway Professorship. The amygdala seemed to the researchers a logical place to start, since it’s a well-established hub for emotion in the brain. Within the amygdala, they narrowed their search by looking for neurons in mice that were active during brief pain stimulation — such as a drop of hot, but not scalding, water applied to a paw. Neurons that are active express more of a specific gene called c-Fos, and indeed, a sea of c-Fos-expressing...
Engineered immune cells target range of pediatric tumors in mice

**By Erin Digitaile**

Immune cells engineered to attack childhood cancers were able to eradicate different types of pediatric tumors in mice, according to a new study from the School of Medicine.

The study, which was published online Jan. 17 in *Clinical Cancer Research*, provides evidence that these engineered cells can target many types of pediatric solid tumors, including brain tumors. Better treatments are badly needed for children with these tumors, particularly when traditional therapies fail.

“The prognosis for children with relapsed brain tumors or solid tumors is generally poor,” said Robbie Majzner, MD, the lead author of the new study and an instructor in pediatrics at Stanford. “We’re excited that we have a potential therapeutic representing a completely new modality to treat these children.”

Majzner’s senior research fellow is Crystal Mackall, MD, the Ernest and Amelia Gallo Family Professor and a professor of pediatrics and of medicine.

Interestingly, although well for adult cancers, some pediatric tumors do not always succeed against childhood cancers, Majzner noted. One approach, called checkpoint inhibition, targets genes that mutate in the most pediatric cancers.

Another immunotherapy method, using chimeric antigen receptor T cells, or CAR-T cells, is the basis of a treatment for lymphoma in adults. Tisagenlecleucel (brand name Yescarta), makes synthetic biology to make immune cells that react to a surface marker found on the leukemias.

**CAR-T for pediatric solid tumors**

Majzner and his colleagues decided to try to make CAR-T cells for pediatric brain tumors and solid tumors, including tumors found in bone and muscle. These tumors do not carry the same surface marker as leukemia, so the scientists’ first step was to look for another marker that engineered immune cells could target.

“Look no higher amounts of the target on the tumor cells, and you may need the target to be on every cell in a tumor,” Majzner said. “The ideal surface marker must not be highly expressed on healthy tissues that prevent engineered immune cells from attacking normal tissues.”

The researchers screened 388 pediatric tumor samples for expression of a surface marker called B7-H3, which prior studies suggested might be a good candidate. B7-H3 was found on 84 percent of the samples, and it was present at high levels in 70 percent of samples. Many types of pediatric cancer were found to express high levels of B7-H3, including Ewing sarcoma (bone), rhabdomyosarcoma (muscle), Wilms tumor (kidneys), neuroblastoma (nerve cells) and medulloblastoma (brain).

The fact that the same marker exists across so many tumor types increases the chance that it could serve as the basis for a commercially viable therapy. Majzner said. Each tumor is fairly rare, with a few hundred children affected across the United States each year, but together they form a larger patient population.

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Activated ‘social’ brain circuits inhibit feeding behavior in mice

By Bruce Goldman

Feeding behavior and social stimulation activate intermingled but distinct brain circuits, and activating one circuit can inhibit the other, according to a new study by researchers at Stanford.

The researchers demonstrated in mice that direct stimulation of fewer than two dozen nerve cells, or neurons, linked to social interaction was enough to suppress the animals’ drive to feed themselves — a finding with potential clinical significance for understanding and treating eating disorders such as anorexia.

The researchers made these findings by developing a technique for teasing apart social and other activity and watching what behavior resulted.

“Over the past decade and a half, Deisseroth’s group focused on a part of the brain called the orbitofrontal cortex, a sheet of cells that, in both mice and humans, lie on the brain’s outer surface toward the front of the organ,” said Deisseroth.

“You know social situations can inhibit the urge to eat,” said Deisseroth. “One example is the behavior of people at different levels of dominance in a social hierarchy. You’re not going to dive into that plate of ribs when you’re dining in the presence of royalty.”

MD, PhD, the D.H. Chen Professor and professor of bioengineering and of psychiatry and behavioral sciences and a Howard Hughes Medical Institute investigator. Lead authorship is shared by postdoctoral scholars Joshua Jennings, PhD, and Christina Kim, PhD, along with staff scientist James Marshel, PhD.

Social curbs on eating behavior

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Food vs. friends

During the experiments that followed, the mice were constrained by an apparatus that kept their heads comfortably fixed in place. In one set of experiments, mice were exposed to a spout that occasionally issued a drop of a high-calorie solution, which could be readily licked up. For each mouse, Deisseroth’s colleagues recorded which orbitofrontal-cortex neurons were active during the high-calorie solution, tying those neurons causally to feeding behavior.

To identify social-responsive neurons in the mice’s orbitofrontal cortex, the scientists introduced juvenile mice — which older mice perceive as nonthreatening potential buddies and set about sniffing — and tracked activity levels in the neurons in the field of view. They were able to identify specific neurons responsive to the exploratory social interaction.

Optogenetically stimulating social-responsive orbitofrontal neurons in the presence of a caloric reward reduced the amount of time the mice spent licking the solution. So did the natural-stimulation equivalent: exposure to juvenile mice. The more the social interaction, the less the interest in calories.

While the mice in this study weren’t a disease model, Deisseroth noted the findings’ potential clinical significance.

“We’ve been able to pinpoint otherwise indistinguishable orbitofrontal-cortex neurons involved in feeding and social drive states,” he said. “A key goal was to know which neurons actually matter for behavior. Now that we do, we can examine them more closely to ask for, say, surface-protein markers or wiring differences that distinguish them from one another. If there are any distinctions like that, that could deepen our understanding of how competing drives are negotiated among neuronal cell types in the cerebral cortex — and could even lead to pharmaceutical interventions that reduce social inhibition of food consumption among people with anorexia.”

Deisseroth is a member of Stanford’s Wu Tsai Neurosciences Institute and of Stanford BioX.

Other study co-authors are graduate student Misha Raffeev; postdoctoral scholar Li Ye, PhD; senior computational and optical systems engineer Sean Quijin, PhD; life science research professional Sally Pak; and life science research assistant Chari Ramakrishnan.

The study was funded by the National Institutes of Health, HHMI, the Defense Advanced Research Projects Agency, the National Science Foundation, the Wiegels Family Fund, the Nancy and James Goodwin Foundation, the Stanley and Betsy Reeves Fund and the H.L. Snyder Foundation.

Stanford’s departments of Bioengineering and of Psychiatry and Behavioral Sciences also supported the work. The Department of Bioengineering is jointly managed by the School of Medicine and School of Engineering.

*Photograph courtesy of Stanford News Service.*

Bladder continued from page 2

ler than could be done with cystoscopy,” Alizadeh said. With the new approach, there is little chance of recurrent bladder cancer, nearly double the sensitivity of cystoscopy and cytology.

The researchers believe that the method of looking for DNA in body fluids other than blood could be more widely applied. “It may eventually be useful for testing saliva for oral cancer, cerebrospinal fluid for neurological cancers or spurn for lung cancer,” Diien said.

Other Stanford co-authors are associate professor of urology Joseph Liao, MD, and professor of pathology Henning Sehe, MD; pathology resident Simon Chen, MD; urology fellow Dharati Treddi, MD; pathology instructor Helo Costa, PhD; postdoc-
toral scholars Mohammad Eshfani, PhD, Mandy Sin, PhD, and Barzin Najafi, PhD; former postdoctoral scholars Aadel Chaudhuri, MD, PhD; medical students William Shi and Daniel Lazareth; former graduate student Jacob Chabon, PhD; research associate Chih Long Liu, PhD; cytologist Harumi Lim; and cytopathology laboratory director Mani Lim.

This research was supported by the Stanford-National Institute of Standards and Technology Joint Institute for Bioanalytical Technology, in Biology, the Stanford Cancer Institute, the Albert Institute for Bladder Cancer Care and Research, the National Cancer Institute, the National Institutes of Health, the Virginia and D.K. Ludwig Fund for Cancer Research and the CRK Faculty Scholar Fund.

Stanford’s departments of Pathology, of Medicine and of Radiation Oncology also supported the work.
Researchers work toward modeling hippocampus in silicon

By Bruce Goldman

In 1953, a 27-year-old Montreal man who’d had frequent seizures even since getting a nasty smack in the head at age 7 underwent surgical removal of brain tissue from the site where his seizures originated. The excised tissue included both of his hippocampi.

The hippocampus is a little horn-shaped structure found on each side of the brain’s midline just above the ears. If you spend enough time staring at a cross section of it on a slide, you may eventually come to see its resembling a seahorse, which is what the Latin term hippocampus means.

In the 1950s, not much was known about the role of the hippocampus — or any other brain structure. That’s actually of some interest, because of patient Henry M. L. H. M. is widely known among neuroscientists as both a cautionary tale and a wake-up call.

Henry, though, his seizures did subside. But for the rest of his long life (he died in 2008 at 82), he could not remember anything new — not a single thing — for more than 30 seconds. His pre-existing biographical memories were unaffected.

“You could have a perfectly lucid conversation with him, walk out of the room to get coffee, come back in and have the same exact conversation all over again,” said Ivan Soltesz, PhD, professor and vice chair of neurosurgery at the Stanford School of Medicine. “For H.M., it was always as if for the first time.”

H.M. could learn new motor skills just fine but couldn’t remember learning them. Plus, his spatial memory was shot. He couldn’t navigate around on his own.

From his experience and many thousands of unrelated experiments, brain scientists and brain surgeons have learned that the hippocampus is both indispensable for learning and memory and, often, the seat where epileptic seizures are initiated.

These features, along with some anatomical and physiological ones that make it easy and exciting to study, have propelled the once-mysterious hippocampus to the fore as arguably the most thoroughly researched part of the brain. Much of this learning has come about by carefully taking the hippocampus apart and analyzing the activities of its components and connections.

“Ivan has, who devotes more than 30 years to understanding how brain circuits work (or don’t), has gone a step further, taking to heart a thought attributed to the late, famed Caltech physicist and Nobel laureate Richard Feynman: ‘If you can build it, you can understand it.”

Soltesz, Stanford Medicine James R. Doty Professor of Neurosurgery and Neuroscience, and his team members are building a full-scale virtual model of a hippocampus.

But unlike a virtual airplane you might see hanging from a 12-inch ceiling, in this model this lives in a computer, in the form of mathematical depictions of neuronal types and their electrochemical components and connections that drive the reception, propagation and handoff of nerve impulses.

The resulting mathematical constructs mimic the component processes that go into a neuron firing off an impulse or its failure to fire one. As a result, the properties of any given individual virtual neuron, or its connections with other virtual neurons, are very similar to what you’d find in its biological counterpart.

“Anything we feed into the model is based on hard experimental evidence,” Soltesz said. “If we’re telling the computer that the firing frequency, strength and duration of this neuron-to-neuron connection should be this much, it’s because that’s what we’ve observed in biological hippocampus and it’s not made up.”

They’ve completed two of its most important sections — about half of the entire structure — and used these components to model their fly-by-wire counterparts. The project, funded by the National Institutes of Health and the National Science Foundation, is steaming along, with plans to complete the model within two or three years.

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The ability to run virtual experiments may also speed up on Blue Waters, a powerful supercomputer hosted by the University of Illinois at Urbana-Champaign,

Blue Waters’ open hardware is designed to perform at least four times faster than any other machine in the world.

They’re using Blue Waters to run virtual experiments.

That, in turn, will enable neuroscientists to get a better handle on how the hippocampus does the mysterious things it naturally does to regulate two crucial cognitive processes. The first is episodic memory (what I had for breakfast, and the second is spatial memory— where I parked the car). If you forget what we ate for breakfast and where we parked the car — and is so particularly prone to the biological deterioration set in motion by Alzheimer’s disease.

It may even lead to better understandings and treat-
Scientists deploy worms to investigate neurological drugs

By Nathan Collins

There are drugs derived from plants to treat epilepsy, to prevent migraines and to halt manic episodes in people with bipolar disorder. But in many cases, no one knows exactly how those and other neurological drugs work — what chemical processes in the brain those drugs alter, or sometimes even what the active ingredients are.

Now, researchers at Stanford and the Carnegie Institution for Science have an unusual idea for how to better understand how those plant-derived drugs work. In the long run, the new project — dubbed NeuroPlant and funded by a Big Ideas grant from the Wu Tsai Neurosciences Institute at Stanford — could also lead to new, more efficient ways to develop drugs to treat a variety of neurological and psychiatric diseases in humans.

“We’re interested in finding out what the mode of action is of these compounds from plants that have known effects on the human nervous system,” said Sue Rhee, PhD, a senior research scientist at the Carnegie Institution for Science and one of NeuroPlant’s principal investigators. “I think it’s an interesting place where we can potentially connect things like ethnomedicine and plant science with neuroscience and perhaps even medicine.”

Observing worm behavior

NeuroPlant is grounded in a simple observation: Plants have a powerful influence on our health and behavior. Around 80 percent of the world’s population relies on herbal medicine for their primary health care, and many modern drugs, including neurological drugs, are derived from plants. That got Rhee wondering: What molecules do plants produce that affect our health and behavior, and what exactly are those molecules doing to us?

In a conversation with Miriam Goodman, PhD, professor of molecular and cellular physiology, Rhee learned that a tiny roundworm called Caenorhabditis elegans could be the perfect platform for studying these questions. For one thing, C. elegans are complete living systems, as opposed to the dis-embodied cells or isolated proteins researchers typically study, meaning that the Neuron team can study their behavior, nervous systems and genetics all at once.

At the same time, C. elegans are much simpler than humans, while sharing a lot of genetic similarities. About 75 percent of the worms’ genes have human equivalents, and their neurons are remarkably similar to humans’ as well. That means what researchers learn about C. elegans stands a decent chance of applying to humans.

With Rhee’s expertise in plant biology, Goodman’s experience with C. elegans sensory systems and the neurobiology and genetics expertise of collaborator Thomas Clandinin, PhD, the Shooter Family Professor and a professor of neurobiology, the group thought they could pioneer a new approach to understanding the neurochemical effects of plant-derived compounds.

The team will start with a large collection of C. elegans worms containing a range of genetic mutations and a plant called valerian, extracts of which are now used in drugs to treat epilepsy and which have been used for thousands of years to treat mild anxiety.

When the team exposes their worms to valerian extracts they’ll watch to see which ones wiggle closer and which flee. As the worms move toward and away from valerian extracts, they will sort themselves according to their genetically encoded responses to those extracts. Once they’ve self-sorted, the researchers can look to see which genes are responsible for that behavior — revealing, in the process, the generic basis of valerian’s effects on the worms. The team will also study how the nervous systems of all of the worms differ from each other. Because humans and roundworms have so many genes in common, these studies should offer hints about how molecules derived from valerian affect humans.

If the experiments with valerian work, the group will branch out to other plants that are the source of neurologic drugs.

A goal: Discover new drugs

The ultimate hope is to use these experiments not just to understand the genetic and neural pathways through which plant extracts and plant-derived drugs work, but also to discover new drugs. Right now, Goodman said, most drugs are developed by screening one small molecule at a time and focusing on just one generic pathway at a time. If NeuroPlant’s approach works, it could allow researchers to screen many potential drugs at a time and look at how those drugs affect a plethora of genetic pathways all at once, potentially speeding the discovery of new treatments.

For now, the aims are more focused. In a year, they hope to have identified a few plant molecules and a few target pathways for those molecules that could explain how a plant like valerian can help treat disease and shape behavior.

“I’m not expecting those chemicals to be drugs” that could actually treat disease, Goodman said. “But if we can identify targets, if we can identify chemicals, it becomes a productive entry point” for a new way to develop new drugs.

Clandinin and Goodman are members of the Wu Tsai Neurosciences Institute and Stanford Bio-X.

Sue Rhee, Thomas Clandinin and Miriam Goodman are team members on the NeuroPlant project, which is using microscopic worms to better understand how plant molecules shape behavior.

**What molecules do plants produce that affect our health and behavior?**

- Plants have a powerful influence on our health and behavior.
- Many modern drugs, including neurological drugs, are derived from plants.
- C. elegans is a simple living system that shares genetic similarities with humans.
- The goal is to understand how plant-derived drugs affect behavior.

**What is the point to make experimentally testable predictions?**

- The team will observe how C. elegans responds to valerian extracts.
- The worms will sort themselves according to their response to the extracts.
- This will help identify chemicals that could be developed into new drugs.

**The hippocampus is divided into compartments that are roughly defined by where excitatory neurons start with the dentate gyrus — transfer information that is essential to forming memories.**

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**Note:** This article is a continuation of the article "Brain: The Neuronal Network" from the January 28, 2019, issue of *Inside Stanford Medicine*. The full story can be found at [insidestanfordmedicine.org](http://insidestanfordmedicine.org).

**Images:**
- "A QYSP/STANFORD NEWS SERVICE"
- "INSIDE STANFORD MEDICINE JANUARY 28, 2019"

**Additional Resources:**
- [Inside Stanford Medicine](http://insidestanfordmedicine.org) for more articles on neuroscience and neurology.
- [NeuroPlant Project](http://neuroplantproject.org) for more information on the research.

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**Inside Stanford Medicine**

January 28, 2019

**Brain continued from page 4**

...and his team have combed the literature for identifying the structures of interest as the thing it’s modeling, is it still a model? It may someday be possible, but why stop there? Other well-funded groups, such as the Allen Institute for Brain Science in Seattle and the Human Brain Project in Switzerland, are also building representations of various aspects of the brain.

"We’re not working in a vacuum," Soltesz said. "I can imagine that in 20 years we can have a mouse and human brains at single-cell resolution." It may someday be possible, Soltesz speculated, to build customized, patient-specific models of the entire brain based on advanced noninvasive imaging and recording techniques, so that the effectiveness of any patient’s best treatment for a given condition or intervention can be tested.

"When a model has as much resolution as the thing it’s modeling, is it still a model? Or is it a working copy?" That’s an excellent question," Soltesz said. "Luckily, we’re nowhere near being able to answer it. It’s pure fantasy right now. But we humans are busily working our way toward that quandary. We’ll deal with it when we get there."
Artery
continued from page 1

The researchers began by looking at newborn mice. They discovered that the young mice have a robust ability to heal injured heart tissue, but they no longer have that ability in adulthood," Red-Horse said. "Understanding what is happening to the arterial endothelial cells during adulthood might explain the inability of arterial endothelial cells to heal in adulthood and of newborn mice with injured hearts.

The scientists monitored the mouse brains with the microscope, watched the mice detect something uncomfortable, observed the aversive reactions and then checked which neurons were active. "With this setup, we identified a set of neurons in the amygdala that selectively encode signals related to the emotional aspects of a painful experience," Schnitzer said. "When the mice touched a drop of uncomfortably hot or cold water (neither of which were severe enough to injure the mice), they withdrew, signaling to the scientist the neuron that did not play a role in their head to record activity in its brain. They positioned the device strategically to visualize the amygdala. The mouse, however, could still stroll as it pleased, while the microscope recorded calcium flux in the neurons, a proxy for cell activity.

The scientists found that the mouse brains with the microscopes on are able to respond to a drop of water that causes any amount of discomfort. When exposed to a drop of hot water, the mice would move their paw back to its original position something that normal mice did not do. This is a crucial part of the harnessing of the ensemble as a tool in pain research. The novelty of this new device is that it allows us to collect calcium flux and monitor the activity of individual neurons to understand the way pain is felt. This tool has the potential to revolutionize pain research and may offer new insights into the mechanisms underlying pain perception and relieve some of the suffering associated with pain.

Schnitzer said that while these findings are promising, they require further investigation to understand the underlying mechanisms and develop targeted therapies for pain management.

Compound identified that may help treat heart failure

By Mandy Erickson

Heart attack survivors may think the worst is behind them. But many later develop heart failure, a progressive disease marked by shortness of breath and swelling in the legs. Symptoms can prevent patients from working, exercising even picking up grandchildren.

Researchers have identified a novel heart attack target when enough of the heart muscle dies, causing the rest of the heart to overwork, which leads to more damage. To protect an overworked, failure-prone heart, cardiologists typically prescribe medications that encourage the heart to pump more slowly, said Ed Mochly-Rosen, PhD, professor of chemical and systems biology and the George D. Smith Professor in Translational Medicine.

Mochly-Rosen is hoping to tackle heart failure at the molecular level. She and her colleagues developed a compound that in preliminary tests appeared to improve heart function in rats with heart failure caused by a heart attack.

The study was published today in *Nature Communications*, Julio Ferreira, PhD, a professor at the University of Sao Paulo and lead author.

One contributor to heart failure following a heart attack is the accumulation of calcium in the heart muscle, said Ely R. Shinagoe, PhD, a postdoctoral scholar in Mochly-Rosen’s lab. "The calcium overload causes the heart muscle fibers to break down and contribute to heart failure. One of those proteins, protein kinase C beta 2, is found in higher levels in failing heart and rodent hearts. The researchers tapped their chemists to develop a compound called SAMBA (pronounced “samba”), which can prevent these proteins from increasing, thereby improving mitochondrial function and providing more energy for the heart.

In tests, post-heart-attack rats that developed heart failure and were treated with SAMBA had better cardiac function measured by how well their left heart ventricles pumped blood with each beat than rats that weren’t treated with SAMBA. "We greatly improved their hearts," Mochly-Rosen said. "If humans are going to be like rats, perhaps we can treat them with a drug that prevents this deterioration."

She added that they also gave healthy rats doses of SAMBA "and it had absolutely no effect," an indication that the compound is specific to heart failure. Mochly-Rosen and Ferreira suspect that SAMBA will also be effective in human heart attack patients. "It could be developed into a drug for human heart attack patients, they believe.

"I’m hopeful SAMBA will be accepted by the industry for drug development because it appears very promising," Mochly-Rosen said.

Longtime Stanford nurse Betty Rose dies at 83

A memorial service for Betty Rose, a nurse who worked at Stanford Hospital for more than 40 years in a variety of leadership roles, will be held at 5 p.m. Jan. 31 at All Saints’ Episcopal Church at 555 Waverley St. in Palo Alto. Betty Rose died Jan. 22 at her home in Palo Alto. She was 83.

In lieu of flowers, donations may be made to the Leducq Foundation (http://elobservador.org), which Rose and her husband Hilbert Morales, who survives her, founded in 1983 to support the Bay Area’s Hispanic community. Her son-in-law’s wedding dress is 1042 West Hedding St., Suite 250, San Jose, CA 95126.
Scientists generate myelin-producing cells, track their growth

By Bruce Goldman

For proper brain function, it’s crucial that certain neurons be wrapped with myelin, a coating that enhances nerve transmission. Failure can spell outcomes ranging from cerebral palsy to multiple sclerosis.

A better understanding of oligodendrocytes, the brain cells that help wrap neurons, may help prevent these diseases. Yet, while cultured neurons have long been scrutinized and manipulated in efforts to pry open their secrets, studying human oligodendrocytes has been stymied. They are born late in brain development, and they’re challenging to generate alongside human neurons and other brain cells in a way that recapitulates the complex interactions occurring among these cell types as they develop.

Now, School of Medicine investigators have proved that stem cells, the workhorse molecules that fuel growing balls of stem-cell-derived human brain cells, which mimic aspects of real brain circuitry, can generate oligodendrocytes together with neurons and a third type of brain cell called astrocytes.

“We now have multiple cell types interacting in one single culture,” said Sergiu Pasca, MD, associate professor of psychiatry and behavioral sciences, “This permits us to look close-up at how the main cellular players in the human brain are talking to each other.”

A study describing the work was published online today in Nature Neuroscience. Pasca, who directs the human brain organogenesis program at the Wu Tsai Neurosciences Institute at Stanford, is the study’s senior author. The lead author is graduate student Rebecca Levy.

From stem cells to oligodendrocytes

In a dish, all three cell types develop from pluripotent stem cells: arrange themselves within three-dimensional balls of brain tissue or spheroids — much as they would in the human forebrain; progressively advance in maturity; and engage in life-like interactions with one another. In the latter case, the Stanford scientists took in on oligodendrocytes’ movements and watched them wrap their extensions around individual neurons to form the insulating coats of myelin that, in real-life organoids, are deployed up and down nerve fibers.

The researchers were able to determine which genes were active at different stages of oligodendrocyte development in the in vitro brain spheroids, and to show that these gene-activation patterns were extremely similar to those of real-life oligodendrocytes at comparable stages of maturation. This enabled them to pinpoint, in these cultured oligodendrocytes, the different times of onset of activation of several genes that, when mutated, cause different genetic disorders associated with myelination defects with possible implications for modeling these disorders.

Many of these brain spheroids, which contain as many as 1 million cells and measure as much as one-eighth of an inch in diameter, have survived in culture for at least two years. During that time, another type of brain cell manifesting the same human genetic mutations, our number neurons in the brain and perform many essen-
tial tasks, from managing nutrition and energy supplies to communicating the brain’s messages, formed in these organoids. “We know that in schizophrenia, myelination, especially in adolescence, is disrupted prior to a patient exhibiting symptoms,” Pasca said.

Sergiu Pasca and his team have proved that a system they developed a few years ago for culturing balls of stem-cell-derived human brain cells can generate oligodendrocytes together with neurons and a third type of brain cell called astrocytes.

Pasca is a member of Stanford’s Maternal & Child Health Research Institute and a faculty fellow of Stanford ChEM-H. Other study co-authors are postdoctoral scholars Yuki Miura, PhD, Qinglin Gu, PhD, and Omer Revah, DVM; former postdoctoral scholar Steven Sloan, PhD; resident physician Rebecca Levy, MD, PhD; and John Huganir, PhD, professor of neurology and neurosciences.

The study was funded by the National Institutes of Health, the National Science Foundation, the MQ Foundation, the Robertson New York Stem Cell Foundation, the Wu Tsai Neurosciences Institute, the Kwan Research Fund, the California Institute for Regenerative Medicine, Stanford Bio-X and the Office of the Dean of the Stanford School of Medicine.

Pasca and Marton are co-authors of a patent that Stanford’s Office of Technology Licensing has filed with the federal government. Stanford’s Department of Psychiatry and Behavioral Sciences also supported the work.

Gun
continued from page 1

45 percent of the bill through Medicaid and, to a lesser extent, Medicare and other public insurance programs, the researchers found.

With most gunshot-wound patients surviving their initial hospital stay, the analysis, which was published online Jan. 23 in PLOS ONE, sheds new light on the long-term costs of firearm injuries and the resulting medical costs.

However, the estimates offer only a piece of the story, as direct medical costs do not include the costs of non-inpatient services, such as medications, rehabilitation, long-term care or home health care, said Thomas Weiser, MD, associate professor of medicine and medical student at Stanford who is the study’s lead author.

“We have begun to look at the long-term costs and future events for medical care,” Spitzer said. “What tends to be forgotten is that the long-term care often affects the injured people’s lives and their needs for care and the financial costs to the health care system.”

Thomas Weiser, MD, associate pro-
fessor of surgery, is the study’s senior author.

Risk of readmission

Examining six years of data from the Healthcare Cost and Utilization Project’s Nationwide Readmissions Database, Spitzer and her colleagues found that 93 percent of the patients initially admitted to the hospital with firearm injuries survived. Most of these patients were discharged after 30 days. However, the researchers found that 9.5 percent of these patients were readmitted within three months of discharge.

The study included 155,574 patients, the study showed that 15.6 percent were readmitted one or more times within six months, for an overall cost of $3,080 being spent on readmissions during the study period. More than half occurred within 30 days of the original discharge.

Risk of readmission was highest for patients who were older, suffered more severe injuries, stayed in the hospital longer during their initial admission and had a psychiatric diagnosis. Patients covered by Medicare had the highest risk of readmission, followed by patients covered by Medicaid.

Self-paying patients were the least likely to be rehospitalized for a firearm injury. Spitzer said this could be because, without insurance coverage, these patients often face full hospital charges that they can’t afford. For example, the average readmission charge for self-paying patients was $49,087. Most live in ZIP codes where the population has incomes lower than average, according to the study.

“Most of the patients are not necessarily think their injuries are less severe,” Spitzer said. “It could be that the patients seek care in circumstances where other patients, who are covered by insurance, would take advantage of their health insurance.”

Hospitalization, readmission costs

Overall, government insurance paid the most for hospitalizations related to firearm injuries during the six-year period according to the study. Of a total $5.47 billion in costs, Medicare contributed $2.1 billion and Medicare provided $389 million. Private insurance and self-paying patients each accounted for about $1.1 billion, while the remainder was covered by other payers.

“On average, the total cost of inpa-
tient hospital care for a patient with a firearm injury was $32,700,” the study found, and readmission accounted for 9.5 percent of that bill.

Spitzer said she hopes the numbers help fill in a larger picture of the ef-
fects of gun violence. She is founder and co-
director of the nonprofit Scrubs Addressing the Firearm Epidemic, or SAFE, which promotes research, education and evidence-based policy as a means to reduce fire-
arm injuries.

“We end up as a society paying a huge amount for these injuries,” Spitzer said. “These numbers draw attention to the fact that there are multiple cures we all face when people are injured by guns.”

Other Stanford co-authors are David Spain, MD, professor of surgery; sur-
gery resident Charlotte Rajasingu, MD, research scientist Lakshika Tennakoon; and medical student Daniel Vail.

The Stanford Medical Scholars Re-
search Program supported this work. Stanford’s Department of Surgery also supported the work.

Steve Dick

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Medical school communications office receives six writing awards

By Susan Ipakitchian

Writers in the School of Medicine’s Office of Communications and Public Affairs received six awards for their work in the Association of American Medical Colleges’ annual competition.

In all, the office received four of the five gold awards in the national contest’s writing categories, along with a silver and a bronze award. The awards were for work published in 2017-18.

Children’s Hospital executive Krista Conger received the gold award in the basic-science writing category for “Eye spy,” a feature that was published in the summer 2017 issue of Stanford Medicine magazine. It describes the journey of Uruguayan-native Alfredo Dubra: As a young boy, Dubra suffered from strabismus, or crossed eyes, and as a medical student, he became a renowned physicist who is spending his life trying to find better ways of examining the retina. “A perfect piece!” the judges wrote. “Well-written, with clear descriptions, a natural flow and wonderful narrative (excellent story and quote to illustrate how people get into a career because of a personal experience).”

Science writer Bruce Goldman received the silver award in the same category for “Brain balls,” a feature in the winter 2018 issue about researcher Sergiu Pasca’s efforts to develop brain organoids that can be grown and studied in the lab. Judges called it a “superb feature” with “evocative explanations of the science. A very enjoyable long read.”

“Magical moment,” which recounted the events surrounding the first U.S. adult heart transplant, earned a gold award in the general staff writing category. The feature was written by Tracie White. Judges cited it as “a model news release” for the current age. “Well-written, with clear descriptions, a natural flow and wonderful narrative (excellent story and quote to illustrate how people get into a career because of a personal experience).”

RUBEN ALVERO, MD, was appointed professor of obstetrics and gynecology, effective Dec. 1. His clinical focus includes infertility, polycystic ovary disease, endometriosis and reproductive surgery. His research aims to improve the understanding and treatment of unexplained infertility.

HARRY GREENBERG, MD, the Joseph D. Grant Professor in the School of Medicine and professor of medicine and of microbiology and immunology, is the recipient of the 2019 Distinguished Achievement Award in Basic Science from the American Gastroenterological Association. The award honors a senior investigator whose work has significantly advanced the science or practice of gastroenterology, or both, and includes a $5,000 honorarium.

ED KOPETSKY, chief information officer of Stanford Children’s Health, was awarded the 2018 John E. Gall Jr. CEO of the Year award by the College of Healthcare Information Management Executives and the Healthcare Information and Management Systems Society. Under Kopetsky’s leadership, Stanford Children’s Health has undergone large-scale advances in enterprise systems and customer service.

NICHOLAS LEEPER, MD, associate professor of surgery and of medicine, has been awarded an Emerging Investigator Award from the American Society for Clinical Investigation. The seven-year, $6 million grant will support his research on clonal expansion, resistance to effectorcytosis (the removal of dead or damaged cells) and innate immunity in atherosclerosis. ROBERT OHGAMI, MD, PhD, was promoted to associate professor of pathology, effective Dec. 1. His research focuses on classifying and understanding hematopoietic diseases such as Castleman disease, acute myeloid leukemia and T- and B-cell disorders using molecular technologies, digital imaging approaches and computational methodologies.

NIDHI ROHATGI, MD, clinical associate professor of medicine, has been named one of the top 10 hospitals of 2018 by ACP Hostpitalist, a publication of the American College of Physicians. The editorial board selected her from nominees across the nation for her dedication to patient care. She was honored for her work improving transitions in care, preventing medical complications in surgical patients and preventing hospital-acquired delirium.

MARIA GRAZIA RONCAROLO, MD, the George D. Smith Professor in Stem Cell and Regenerative Medicine and professor of pediatrics and of medicine, received the 2019 Translational Pioneer Award from Cell & Gene Therapy Insights. The award recognizes the contributions of her translational research studies, which have led to greater understanding of the mechanisms underlying immune tolerance in stem cell transplantation, and have been fundamental to the development of novel stem cell and gene therapies for patients with genetic and acquired diseases of the hematopoietic and immune systems.

LISA SIEH, MD, PhD, clinical professor of medicine, and DAVID SVEC, MD, MBA, clinical assistant professor of medicine, received the Malinda Mitchell Award from Stanford Health Care for their work to decrease inappropriate use of intermediate intensive care unit level care. The award, which recognizes excellence in quality and service, is named for the former president and chief executive officer of Stanford Health Care.

MANPREET SINGH, MD, was promoted to associate professor of psychiatry and behavioral sciences, effective Nov. 1. She directs the Stanford Pediatric Mood Disorders Program. Her work focuses on characterizing the origins and pathways for developing mood disorders, and conducting translational research to protect and preserve brain function after symptoms begin. In addition, she was selected to receive the 2019 American Psychiatric Association’s Blanche F. Etelson Award, which includes a $2,000 honorarium and recognizes a psychiatrist whose work has had significant impact on children and adolescent psychiatry.

NICHOLAS LEEPER, MD, PhD, assistant professor of medicine, has joined the Endocrine Society’s leadership team as a member of its council. In her role representing basic science, she will work toward the society’s mission to promote optimal health by advancing endocrine science, education and care.

Megan Albertelli
Ruben Alvero
Harry Greenberg
Ed Kopetsky
Nicholas Leeper
Rupert Ohgami
Nidhi Rohatgi
Maria Grazia Roncarolo
Lisa Siew
David Svec
Manpreet Singh
Jay Wu

An award-winning story described how Alfredo Dubra went from a child with strabismus, or crossed eyes, to a physicist working to find better ways of examining the retina.