INSIDE STANFORD MEDICINE

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Medical students are helping organize an effort to send letters of support to Syrian refugees living in Jordan.

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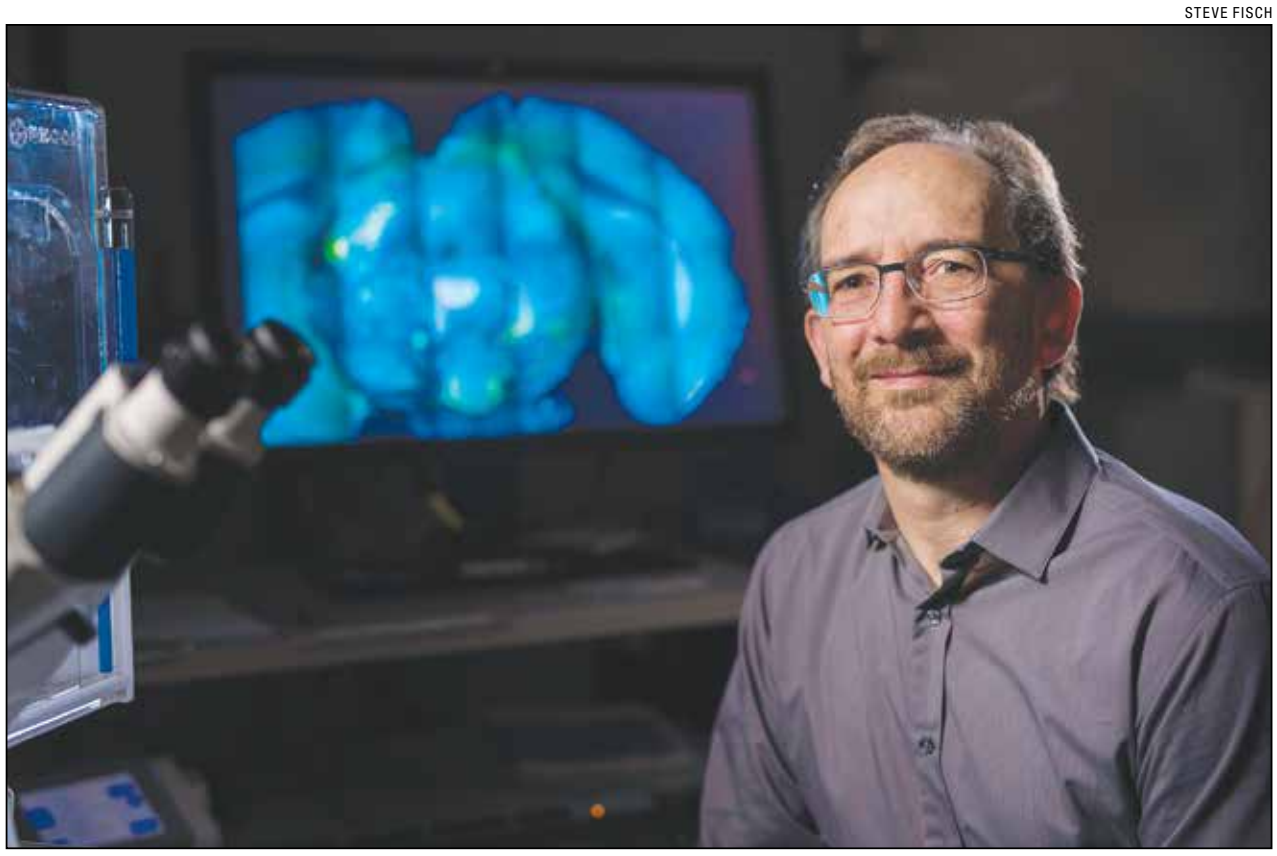
How slow, deep breaths induce tranquility

By Bruce Goldman

STEVE FISCH



Mark Krasnow and his colleagues have identified a tiny cluster of neurons that link breathing to relaxation, attention, excitement and anxiety. The cluster is located in an area that Krasnow calls the pacemaker for breathing.

Try it. Breathe slowly and smoothly. A pervasive sense of calm descends. Now breathe rapidly and frenetically. Tension mounts. Why?

It's a question that has never been answered by science, until now.

In a new study, researchers at the School of Medicine and their colleagues have identified a handful of nerve cells in the brainstem that connect breathing to states of mind.

A paper describing the findings was published March 31 in *Science*. Mark Krasnow, MD, PhD, professor of biochemistry, is the senior author. The lead author is former Stanford graduate student Kevin Yackle, MD, PhD, now a faculty fellow at UC-San Francisco.

Medical practitioners sometimes prescribe breathing-control exercises for people with stress disorders. Similarly, the practice of pranayama — controlling breath in order to shift one's consciousness from an aroused or even frantic state to a more meditative one — is a core component of virtually all varieties of yoga.

"This study is intriguing because it provides a cellular and molecular understanding of how that might work," Krasnow said.

Tiny cluster of neurons

The tiny cluster of neurons linking respiration to relaxation, attention, excitement and anxiety is located deep in the brainstem. This cluster, located in an area Krasnow calls the pacemaker for breathing, was discovered in mice by study co-author Jack Feldman, PhD, a professor of neurobiology at UCLA, who published his findings in 1991. An equivalent structure has since been identified in humans.

"The respiratory pacemaker has, in some respects, a tougher job than its counterpart in the heart," said Krasnow, who is also a Howard Hughes Medical Institute investigator. "Unlike the heart's one-dimensional, slow-to-fast continuum, there are many distinct types of breaths: regular, excited, sighing, yawning, gasping, sleeping, laughing, sobbing. We wondered if different subtypes of neurons within the respiratory control center might be in charge of generating these different types of breath."

On that hunch, Yackle searched through public databases to assemble a list of genes that are preferentially activated in the part of the mouse brainstem where the breathing-control center resides. This center's technical term is the pre-Bötzinger complex, or preBötC.

He pinpointed a number of such genes, allowing the investigators to identify more than 60 separate neuronal subtypes, physically differentiated by their gene-activation signatures but comingling in the preBötC like well-stirred spaghetti strands. The scientists were able to use these genes, and the protein products for which they are recipes, as markers allowing them to zero in on the different neuronal subtypes.

Knocking out neurons

Now the scientists could systematically assess the role of each neuronal subpopulation in laboratory mice. With advanced technologies, they could selectively destroy any one of these neuronal subtypes — and only that subtype — based on its unique signature of active genes. Then they could observe how this particular subtype's loss affected the animals' breathing.

In 2016, in collaboration with Feldman, they succeeded in isolating a subpopulation of neurons in the preBötC that explicitly controls See KRASNOW, page 6

Stores of monounsaturated fat help pudgy worms outlive skinny worms

By Krista Conger

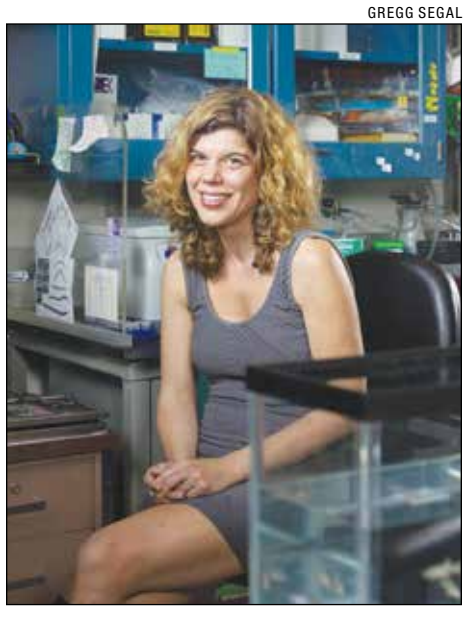
Pudgy roundworms storing a particular type of fat live longer than their more svelte counterparts, according to a study by researchers at the School of Medicine.

This fatty buildup, and the subsequent increase in the worms' life span, can be stimulated simply by feeding the animals monounsaturated fatty acids like those found in olive oil. Because many species share similar patterns of fat metabolism, it's possible that the findings could extend to other animals, including humans, the researchers believe.

The finding suggests that accumulating a specific type of fat can actually be beneficial. It came as a surprise to the researchers because severe caloric restriction has also been shown to extend the life span of many animals.

"We have known for some time that metabolic changes can affect life span, but we expected the long-lived animals in our study would be thinner," said Anne Brunet, PhD, professor of genetics. "Instead, they turned out to be fatter. This was quite a surprise."

GREGG SEGAL



Anne Brunet and her team were surprised to find that pudgy roundworms with stores of monounsaturated fat outlived thinner worms.

Brunet, who is also an associate director of Stanford's Paul F. Glenn Center for the Biology of Aging, is the senior author of the study, which See BRUNET, page 6

Packard Children's heart center will benefit from Moores' $50 million gift

By Jennifer Yuan

Lucile Packard Children's Hospital Stanford has received a gift of $50 million from Gordon and Betty Moore to deliver exceptional patient care and advance research that improves the health of children with heart disease.

The Moores' donation is the largest private gift to Lucile Packard Children's Hospital Stanford since the hospital's founding donation from David and Lucile Packard.

In honor of the new gift, Packard Children's internationally renowned Children's Heart Center will be named the Betty Irene Moore Children's Heart Center. The gift provides funding for clinical and research facilities, an endowment for the center's highest strategic priorities and endowed positions for faculty to lead specialized care and research.

Gordon Moore is co-founder of Intel Corp. He and his wife, Betty, are also founders of the Gordon and Betty Moore Foundation, which works to create positive outcomes for future generations. They are longtime supporters of Packard Children's and previously made gifts to enable the hospital's 521,000-square-foot expansion, which is now nearing completion.

The Moores were motivated to make their latest gift See MOORE, page 7

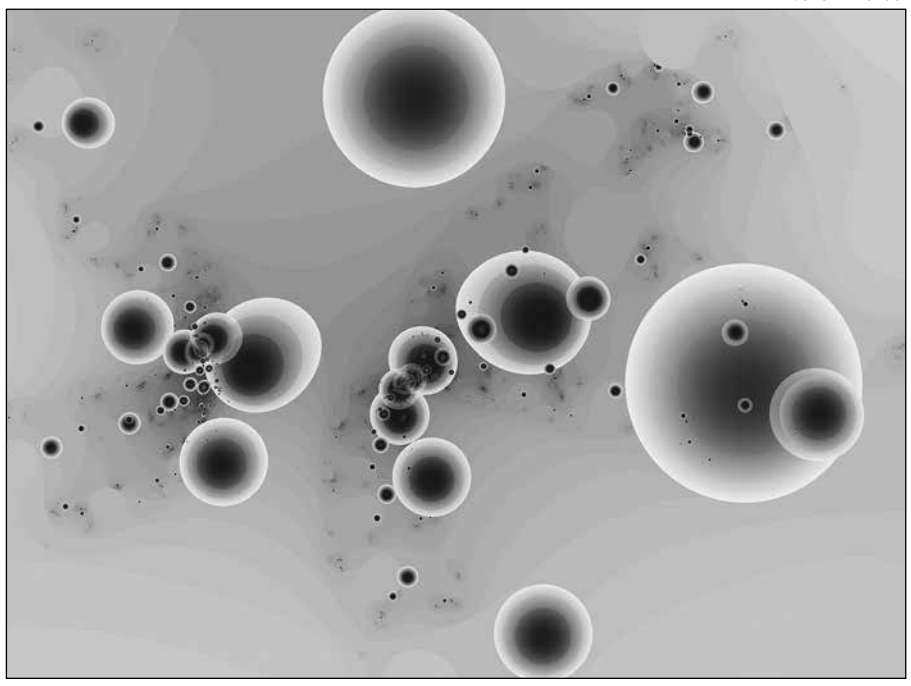
COURTESY OF SUSANNA FROHMAN/MERCURY NEWS

Gordon and Betty Moore say their gift was motivated by a grandchild's care at the hospital.

Ultrasound and microbubbles flag malignant cancer in humans

By Jennie Dusheck

ARVIND BALARAMAN/SHUTTERSTOCK



Researchers at the School of Medicine have improved on microbubbles so that they bind to malignant tumors, making the tumors visible to ultrasound imaging.

A team led by researchers from the School of Medicine has demonstrated a way to diagnose cancer without resorting to surgery, raising the possibility of far fewer biopsies.

For the study — a first-in-humans clinical trial — which was published online March 14 in the *Journal of Clinical Oncology,* women with either breast or ovarian tumors were injected intravenously with microbubbles capable of binding to and identifying cancer.

Jürgen Willmann, MD, a professor of radiology at Stanford, is lead author, and Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology, is the senior author.

For the study, 24 women with ovarian tumors and 21 women with breast tumors were intravenously injected with the microbubbles. Clinicians used ordinary ultrasound to image the tumors for about a half-hour after injection. The high-tech bubbles clustered in the blood vessels of tumors that were malignant, but not in those that were benign.

The ultrasound imaging of patients' bubble-labeled tumors was followed up with biopsies and pathology studies that confirmed the accuracy of the diagnostic microbubbles.

What are microbubbles?

Medical microbubbles are spheres of phospholipids, the same material that makes up the membranes of living cells. The bubbles are 1 to 4 microns in diameter, a little smaller than a red blood cell, and filled with a harmless mixture of perfluorobutane and nitrogen gas.

Ordinary microbubbles have been approved by the Food and Drug Administration and in clinical use for several years now. But such microbubbles, a kind of ultrasound "contrast agent," have only been used to image organs like the liver by displaying the bubbles as they pass through blood vessels. Up to now, the bubbles couldn't latch onto blood vessels of cancer in patients.

Safe but better microbubbles

The microbubbles used in this study were designed to bind to a receptor called KDR found on the tumor blood vessels of cancer but not in healthy tissue. Noncancerous cells don't have such a receptor. Under ultrasound imaging, the labeled microbubbles, called MB_{KDR}, show up clearly when they cluster in a tumor. And since benign breast and ovarian tumors usually lack KDR, the labeled microbubbles mostly passed them by.

In this small, preliminary safety trial, the technique appeared to be both safe and very sensitive, said Willmann, who is chief of the Division of Body Imaging at Stanford. And it also works with ordinary ultrasound equipment. "So, there's no new ultrasound equipment that needs to be built for that," he said. "You can just use your regular ultrasound and turn on the contrast mode — which all modern ultrasound equipment has."

Sanjiv Gambhir

Jürgen Willmann

Willmann said now that the phase-1 trial has shown that the MB_{KDR} contrast agent is safe for patients, his team is moving forward in a larger phase-2 trial. In that trial, the team will measure how well the combination of MB_{KDR} and ultrasound differentiate cancer from noncancer in breast and in ovarian tumors. The team will also try to find out how small a tumor can be imaged using KDR microbubbles. Because the diagnostic approach can, in principle, be used with any kind of cancer that expresses KDR, they plan to image pancreatic cancer tumors as well.

One of the advantages of MB_{KDR}, Willmann said, is that the bubbles remain attached to the tumors for several minutes and as long as half an hour — the longest time tested in the trial. That should give clinicians time to image both breasts or both ovaries without having to start over with a new injection of contrast agent.

If all goes as hoped, the KDR microbubbles could improve diagnoses and reduce unnecessary surgeries in women suspected of having breast or ovarian cancer.

"The difficulty with ultrasound right now," Willmann said, "is that it detects a lot of lesions in the breast, but most of them are benign. And that leads to many unnecessary biopsies and surgeries."

Distinguishing benign from malignant tumors with harmless ultrasound imaging could save millions of patients from biopsies they don't need, Willman said.

"To decrease those unnecessary biopsies and surgeries would be a huge leap forward," he said. "We could make ultrasound a highly accurate screening technology that is relatively low cost, highly available and with no radiation."

And since ultrasound technology is accessible almost everywhere, he said, the technology could potentially help patients all over the world.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford-affiliated co-authors of the study are assistant professor of radiology Amelie Lutz, MD, and research assistant Keerthi Valluru.

Gambhir is director of the Canary Center for Cancer Early Detection at Stanford, director of the Molecular Imaging Program at Stanford and a member of Stanford Bio-X. Willmann is a member of Stanford Bio-X, the Molecular Imaging Program and the Canary Center. Lutz is a member of Stanford Bio-X.

Researchers from the Gemelli University Hospital in Rome are also co-authors of the study.

The research was supported by the National Institutes of Health, the Bracco Group and the Canary Foundation.

Stanford's Department of Radiology also supported the work. ISM

Stanford researchers seeking teens, young adults with autism for clinical trial of drug that may reduce aggressive behaviors

By Erin Digitale

Researchers at the School of Medicine are seeking teenagers and young adults ages 14 to 21 to participate in a clinical trial of a compound, pregnenolone, that may reduce irritability and associated aggressive behaviors in autism spectrum disorder.

Irritability and aggressive behavior are the No. 1 reason that individuals with autism end up in emergency rooms. Without effective treatment, these behaviors can cause significant problems in daily life for people with autism and their families.

But available treatments have drawbacks.

"The atypical antipsychotic medications we use to treat mood dysregulation in autism have a lot of side effects," said lead investigator Antonio Hardan, MD, professor of psychiatry and behavioral sciences. The long-term side effects can include diabetes and involuntary motor movements.

Pregnenolone is a neurosteroid that has previously been shown to alleviate symptoms of other psychiatric conditions such as schizophrenia. Neurosteroids are naturally occurring steroid hormones synthesized in the brain and other organs. Recently, researchers have begun to understand their roles in sending signals to nerves in the brain.

Antonio Hardan

"The biology of neurosteroids in other psychiatric disorders has been studied for about 20 years, but in autism not much is known," said study investigator Lawrence Fung, MD, PhD, an instructor in psychiatry and behavioral sciences. "This study will give us a chance to understand their role in the pathophysiology of autism." The trial may also enable the future development of biomarkers for autism, he said.

Some scientists hypothesize that individuals with autism have too much excitatory signaling or too little inhibitory signaling, or both, in their brain circuits. Metabolites of pregnenolone have been shown to increase inhibitory signaling. Thus, pregnenolone may benefit people with autism by "normalizing" the imbalance between excitatory and inhibitory signaling; it could possibly help treat mood dysregulation, sensory abnormalities and social deficits.

"Pregnenolone is very benign and usually very well-tolerated," Hardan said. "Patients should know that the potential for benefit is modest, but we think it is still worth exploring its value in treating individuals with autism."

Teens and young adults aged 14 to 21 with autism are eligible to enroll in the trial. Study participants will visit Stanford once every two weeks for the 14-week trial. Participants will be randomized to receive either pregnenolone or placebo and will not know which compound they receive until the 14-week period is over. After that, the subjects who receive placebo in the randomized phase will have the option to start taking pregnenolone.

More information about the trial is available at http://med.stanford.edu/autism or by calling (650) 736-1235. ISM

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STANFORD MEDICINE

Nerve cells actively repress alternative cell fates, study shows

By Krista Conger

A neural cell maintains its identity by actively suppressing the expression of genes associated with non-neuronal cell types, including skin, heart, lung, cartilage and liver, according to a study by researchers at the School of Medicine.

It does so with a powerful repressor protein. "When this protein is missing, neural cells get a little confused," said Marius Wernig, MD, associate professor of pathology. "They become less efficient at transmitting nerve signals and begin to express genes associated with other cell fates."

The study marks the first identification of a near-global repressor that works to block many cell fates but one. It also suggests the possibility of a network of as-yet-unidentified master regulators specific to each cell type in the body.

"The concept of an inverse master regulator, one that represses many different developmental programs rather than activating a single program, is a unique way to control neuronal cell identity, and a completely new paradigm as to how cells maintain their cell fate throughout an organism's lifetime," Wernig said.

Because the protein, Myt1l, has been found to be mutated in people with autism, schizophrenia and major depression, the discovered mode of action may provide new opportunities for therapeutic intervention for these conditions, the researchers said.

Wernig is the senior author of the study, which was published April 5 in *Nature*. Postdoctoral scholars Moritz Mall, PhD, and Michael Kareta, PhD, are the lead authors.

Repressors

Myt1l is not the only protein known to repress certain cell fates. But most other known repressors specifically block only one type of developmental program, rather than many. For example, a well-known repressor called REST is known to block the neuronal pathway, but no others.

"Until now, researchers have focused only on identifying these types of single-lineage repressors," said Wernig. "The concept of an 'everything but' repressor is entirely new."

In 2010, Wernig showed that it is possible to convert skin cells into functional neurons over the course of three weeks by exposing them to a combination of just three proteins that are typically expressed in neurons. This "direct reprogramming" bypassed a step called induced pluripotency that many scientists had thought was necessary to transform one cell type into another.

> "The concept of an 'everything but' repressor is entirely new."

One of the proteins necessary to accomplish the transformation of skin to neurons was Myt1l. But until this study the researchers were unaware precisely how it functioned.

"Usually we think in terms about what regulatory programs need to be activated to direct a cell to a specific developmental state," said Wernig. "So we were surprised when we took a closer look and saw that Myt1l was actually suppressing the expression of many genes."

These genes, the researchers found, encoded proteins important for the development of lung, heart, liver, cartilage and other types of non-neuronal tissue. Furthermore, two of the proteins, Notch and Wnt, are known to actively block neurogenesis in the developing brain.

Blocking Myt1l expression in the brains of embryonic mice reduced the number of mature neurons that developed in the animals. Furthermore, knocking down Myt1l expression in mature neurons caused them to express lower-than-normal levels of neural-specific genes and to fire less readily in response to an electrical pulse.

'A perfect team'

Wernig and his colleagues contrasted the effect of Myt1l with that of another protein called Ascl1, which is required to directly reprogram skin fibroblasts into neurons. Ascl1 is known to specifically induce the expression of neuronal genes in the fibroblasts.

"Together, these proteins work as a perfect team to funnel a developing cell, or a cell that is being reprogrammed, into the desired cell fate," said Wernig. "It's a beautiful scenario that both blocks the fibroblast program and promotes the neuronal program. My gut feeling would be that there are many more master repressors like Myt1l to be found for specific cell types, each of which would block all but one cell fate."

Wernig is a member of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, Cardiovascular Institute, Child Health Research Institute, Cancer Institute, Neurosciences Institute and Bio-X.

Other Stanford co-authors of the paper are postdoctoral scholars Soham Chanda, PhD, Bo Zhou, PhD, Xuecai Ge, PhD, and Philip Brennecke, PhD; graduate students Cheen Ang, Thomas Vierbuchen and Daniel Fuentes; research assistant Sarah Grieder; undergraduate student Brandon Walker; professor of genetics Lars Steinmetz, PhD; and professor of molecular and cellular biology Thomas Sudhof, MD.

The research was supported by the German Research Foundation, the National Institutes of Health, the California Institute for Regenerative Medicine, the New York Stem Cell Foundation, the Howard Hughes Medical Institute, the Swedish Research Council, the Swedish Government Initiative for Strategic Research Institute, the Department of Health and Human Services and the Spectrum Child Health Research Institute.

Stanford's Department of Pathology also supported the work. **ISM**

STEVE FISCH

The findings by Marius Wernig and his team suggest that there are many master regulators that help cell types maintain their identities — a concept that Wernig calls a new paradigm.

Four research teams receive grants for cancer immunotherapy projects

By Ruthann Richter

The Parker Institute for Cancer Immunotherapy at Stanford has awarded its first round of bench-to-bedside grants to four research teams at the School of Medicine.

These grants are designed for faculty with early-stage projects in cancer immunotherapy that might not be funded through traditional sources. Each team, consisting of both basic science and clinical investigators, will receive $200,000 over two years.

The awards were selected from a pool of 27 proposals by a committee of Stanford experts led by Crystal Mackall, MD, the institute's director at Stanford and a professor of pediatrics and of medicine.

The grantees and their projects are:

• John Sunwoo, MD, assistant professor of otolaryngology, and his team are looking at why a form of immune therapy known as a checkpoint blockade produces a significant response among some patients, but not others. They plan to use a positron emission tomography tool, as well as MRI, to help predict which patients with head and neck squamous cell carcinoma are most likely to develop a positive immune response. His colleagues are Olivier Gevaert, PhD, assistant professor of medicine; Dimitrios Colevas, MD, professor of medicine; and Nancy Fischbein, MD, professor of radiology.

• Robert Negrin, MD, professor of medicine, and his colleagues are investigating why some blood cancer patients who are treated with T-cell-based immunotherapy develop rejection. He and Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology, have developed a PET imaging strategy that they will use to study these cells, with the goal of predicting which patients are likely to accept, or reject, the therapy. Sally Arai, MD, associate professor of medicine, is also part of the team.

• Ash Alizadeh, MD, PhD, assistant professor of medicine, and Russ Altman, MD, PhD, professor of bioengineering, of genetics and of medicine, are studying cancer antigens — molecules that induce an immune response and that are key to controlling or curing cancer. They are developing a method for predicting which tumor antigens are most likely to be useful in this process. Their team includes graduate student Binbin Chen and research scientist Chih Long Liu, PhD.

• Wendy Fantl, PhD, assistant professor of obstetrics and gynecology, and her group will be using CODEX, an imaging platform invented at Stanford, to determine the key biomarkers that will predict which patients with renal cancer will respond to a form of cancer immunotherapy. Her colleagues are John Leppert, MD, assistant professor of urology; senior research scientist Veronica Gonzalez, PhD; and research scientist Nikolay Samusik, PhD.

The institute was established last year as part of an initiative, funded by Silicon Valley pioneer and philanthropist Sean Parker, to develop innovative approaches to cancer by capitalizing on the power of the immune system. Stanford is one of six academic medical centers in the venture, which works through a highly collaborative process. **ISM**

Academic, industry, government experts will convene for med school's April 24 conference on drug discovery

The 2017 Stanford Drug Discovery Conference will take place April 24 from 8:30 a.m. to 6 p.m. at the medical school's Li Ka Shing Center for Learning and Knowledge.

The conference brings together a variety of experts in drug discovery to discuss policy, research and venture topics. Speakers include leaders in the field from academia, industry and government.

The two keynote speakers are Nobel laureate Thomas Sudhof, MD, PhD, Stanford professor of molecular and cellular physiology, who will discuss "Why understanding and treating neuropsychiatric disorders is so difficult," and former FDA commissioner Robert Califf, MD, who will speak on, "Key elements of the drug development ecosystem."

The event is free and open to the public. For more information or to register, visit the Stanford Cardiovascular Institute website at http://med.stanford.edu/cvi.html. **ISM**

Special delivery: Sending letters of support to Syrian refugees

By Ruthann Richter

In the video, Raneem, a Syrian refugee living in Jordan, is shown reading aloud a letter of support from a staff member at the School of Medicine. The 18-year-old woman, wearing a black head scarf and plaid dress, pauses at one point, bows her head and wipes away tears.

"She gave me motivation and hope," Raneem said of the letter writer. "It felt like someone is sharing the same ambitions with me."

The writer, Laila Soudi, is a research assistant in global mental health who is spearheading a campaign to encourage members of the Stanford community to write to Syrian refugees who have fled their country's violence. She is partnering with CARE International, a humanitarian nonprofit organization, which produced the video and will deliver the letters to refugees living in camps and in urban centers in Jordan.

"These are letters of solidarity and support," Soudi said in an interview. "We have to be careful in not overpromising anything. But our message is that we understand you exist and your voices are silenced, but we are here to support you in any way we can. You are not alone."

Soudi and a coalition of medical and undergraduate students aim to engage as many people as possible across the Stanford campus in composing letters that will be delivered to the refugees, particularly children and teenagers.

Letter-writing event

They are organizing a mass letter-writing event April 20 in Room M114 of the medical school's Alway Building and at The Markaz, a campus resource center for Stanford's Muslim community. Letter-writers can also send their expressions of support online at: https://my.care.org/site/SPageNavigator/CARE_SpecialDelivery.html.

DALA ABU RAGHEB

Laila Soudi plays with Syrian refugee children during a visit to the King Abdullah Park Refugee Camp in Jordan. She says many of the children suffer from the trauma of their country's devastating civil war.

Soudi said the campaign was inspired by her experiences working with refugees in Jordan, where some 2 million Syrians have sought shelter from their country's devastating civil war in what some have called the world's worst humanitarian crisis in decades. She said many, like Raneem, are still suffering from the trauma of seeing their family members murdered and their homes destroyed. Her research in the laboratory of Victor Carrion, MD, a professor of psychiatry and behavioral sciences, focuses on the impact of this trauma on the mental health of children and adolescents.

The campaign is also a personal one: Soudi, a native of Syria, said she has much in common with Raneem, whose goal is to become a pharmacist so she can help others, particularly Syrian children.

"I feel like I am talking to somebody who could very well be my sister," Soudi said.

Some student leaders of the campaign said they felt compelled to act in light of the Trump administration's proposed ban on travel from several Muslim-majority countries, including Syria, a move that many have condemned for putting Muslim communities under a cloud of suspicion and sending a message to refugees that they are unwanted.

"This year especially, with refugees being vilified by the administration and the media, I think it's very important to take action around refugees, humanizing them and letting the world know, letting America know, letting Stanford know that these are human beings worthy of an opportunity," said Osama El-Gabalawy, a first-year Stanford medical student from Seattle who is involved in the effort.

Other students say they have watched the unfolding of the Syrian crisis with horror and felt paralyzed by their inability to intervene.

"I feel really powerless on this end. We care a lot and we see these horrible things happening, and there is not much we can do without endangering ourselves," said Yagmur Muftuoglu, a first-year medical student who is helping to organize the letter-writing event. "But I see the letter as something we can possibly do, something that might bring somebody a bit of recognition for the horrible things they've experienced. As medical students here, we are so blessed. Being able to do nothing about it is something I sit with every day."

Thinking of them

Muftuoglu said she and other medical students had been looking for a meaningful way to help refugees and had considered traveling to Jordan to provide direct support. But she questioned whether "dropping in" for a week or two on a humanitarian mission would be a meaningful way to contribute.

"It's not necessarily that a letter-writing campaign will change someone's life," said Muftuoglu, a native of Turkey. "But we want these people to know we are thinking of them — that they mean something important to us and their lives are dear."

She, El-Gabalawy and others are working with undergraduates and with fellow graduate students in law and business to engage them in the campaign. They hope to gather between 200 and 300 letters, which will be translated into Arabic by student volunteers, El-Gabalawy said.

"We are excited about getting our peers involved and showing them that if you are frustrated by paralysis of action, there are always avenues. It can be as simple as writing a letter. A big part is breaking out of that paralysis and realizing that your voice can be very powerful," El-Gabalawy said.

He believes the campaign will be particularly appealing to medical students, whose mission is to guard the health of others.

"Recognizing someone's humanity is the most essential step in caring for their health," he said. **ISM**

New insulin delivery systems for Type 1 diabetes come of age

By Andrew Schwartz

At 19 months old, Jamie Kurtzig was diagnosed with Type 1 diabetes. For the next 10 years, her parents would wake up every three hours during the night to prick their daughter's finger so they could check her blood glucose level.

If her blood glucose was too low, they gave her food to avoid seizures or a loss of consciousness. If it was too high, they gave her an insulin injection to bring the level down to a normal range.

"It's caused a kind of PTSD for my husband and me," said Sara Kurtzig, who lives with her daughter and husband in Marin, California.

But for the past year, they've been able to sleep through most nights. That's because Jamie started using a hybrid closed-loop insulin delivery system in 2016, thanks to a clinical trial at Lucile Packard Children's Hospital Stanford and Stanford Medicine that assessed the system's use in children ages 7 to 14.

"The closed-loop system has completely changed our lives," Sara said. "It took me a month to trust it, but now I can go to bed at 11 p.m. and wake up at 6:30 a.m. almost every night."

The system is among the methods being tested by researchers at the School of Medicine and Lucile Packard Children's Hospital in their efforts to find easier ways for younger children with Type 1 diabetes to get the doses of insulin they need.

Bruce Buckingham, MD, professor of pediatric endocrinology, directs clinical trials of the closed-loop system, which modulates insulin delivery based on glucose sensor readings measured every five minutes. He called the system a "historic advance" for diabetes care.

"With this system, patients can achieve very reliable and safe overnight glucose control, mitigating overnight highs and lows with minimal manual intervention," said Buckingham, who treats patients at Packard Children's. The improved glucose control dramatically decreases the risk for overnight seizures and long-term complications associated with Type 1 diabetes.

Bruce Buckingham

Type 1 diabetes is an autoimmune disease in which the body's immune system attacks insulin-producing cells in the pancreas. As a result, the pancreas produces little or no insulin, a hormone that brings glucose from the bloodstream into the body's cells to be used as energy.

Without insulin, the body cannot use glucose as energy. Too much insulin can cause severe low blood glucose levels, which can result in seizures, loss of consciousness and, in worst-case scenarios, death. Too little insulin can lead to high blood glucose levels and long-term complications. That's why people with Type 1 diabetes have to frequently check their glucose levels.

Clinical trials lead to FDA-approved devices

In September 2016, an article in the *Journal of the American Medical Association* detailed the successful multicenter trial of a hybrid closed-loop insulin delivery system for patients with Type 1 diabetes over the age of 14. Later that month, the FDA announced approval of the device tested in the study, the Medtronic MiniMed® 670G system, for that age group.

The system, commonly referred to as an artificial pancreas, works by wirelessly linking an insulin pump and a glucose monitor. While some of the testing and blood-sugar adjustments can be made by the system, patients must still perform these tasks themselves prior to eating.

Buckingham, a co-author of the article, receives research support from Medtronic. He noted that Stanford conducted the initial studies on this system at a camp for children with diabetes in 2014.

"We are not yet to the point where these systems have been tested in all age groups or where they truly mimic all functions of a human pancreas, so there is more work to do," said Buckingham.

Among the challenges: Current hybrid closed-loop systems still require patients to assess the amount of food (carbohydrates) they are eating and to deliver an insulin dose through their pump before meals.

Buckingham and his closed-loop team at Stanford continue to work toward improving the system. Their efforts include testing and adapting these devices for younger children as well as testing systems with different user interfaces and different methodologies that adjust for exercise and insulin delivery at meals.

Helping younger patients and their families

The hybrid closed-loop system has other advantages, as well. Twelve-year-old Jamie Kurtzig, now old enough to want the freedom to do things like attend sleepovers at a friend's house,

See CLOSED-LOOP, page 5

New insights into complexity of brain's navigation system

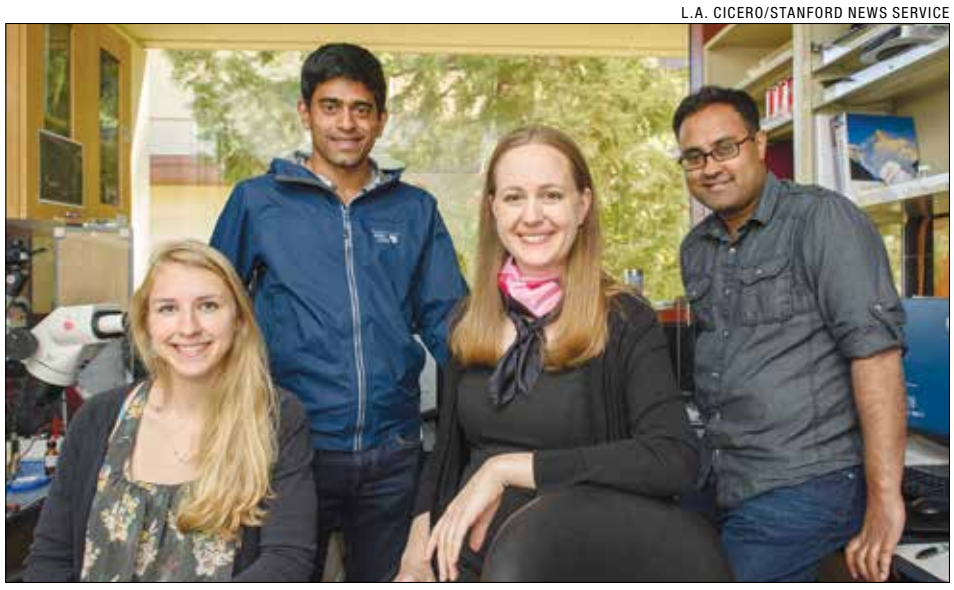
By Nathan Collins

Just like a driver in a car, the brain needs some basic navigational instruments to get around, and it is not an idle analogy. In fact, scientists have found brain cells that are similar to speedometers, compasses, GPS and even collision warning systems.

That simple analogy, however, may belie the more complex way our brains actually map out the world, Stanford researchers report April 6 in *Neuron*. While some of the neurons in our internal navigation systems look a lot like speedometers or compasses, many others operate flexibly, each one encoding a dynamic mix of navigational variables, like a compass that somehow transforms into a GPS when driving downtown.

It's a discovery that could change the way we think about navigation in the brain, said Lisa Giocomo, PhD, assistant professor of neurobiology in the School of Medicine and member of Stanford Bio-X and the Stanford Neurosciences Institute. In fact, it might even challenge one of our most basic assumptions about how neurons work.

L.A. CICERO/STANFORD NEWS SERVICE



Graduate students, from left, Kiah Hardcastle and Niru Maheswaranathan, worked with professors Lisa Giocomo and Surya Ganguli on a study of the brain's navigational neurons.

Beginning at the boundary

The project began in 2014 when Giocomo and Surya Ganguli, PhD, assistant professor of applied physics, got a Bio-X seed grant to take a closer look at how the brain finds its way around. It was the same year a Nobel Prize was awarded for the discovery of grid cells, specialized neurons that help animals keep track of where they are in their environments. At the time, they were hailed as the brain's GPS.

But something was off: While some neurons fell within the ballpark of how a grid cell was supposed to behave, most provided only noisy, error-prone navigation, like a GPS on the fritz. That led Ganguli, Giocomo and graduate student Kiah Hardcastle to wonder whether the brain had a way to correct those errors.

As it turns out, the brain does have a way: boundary cells, so named because they fire when nearing walls and other landmarks. By tracking neuron firing in mice as they walked around a square box, Hardcastle, Ganguli and Giocomo found that boundary cells help reset wayward grid cells, much like stumbling on a familiar spot helps reorient someone who had been hopelessly lost.

That finding, published in 2015, was significant in its own right — until then, no one understood how grid cells could track position error-free over long distances. But something more surprising was in store.

A left turn

At first, the group — now including graduate student Niru Maheswaranathan — just wanted to see what else boundary cells might be up to, Hardcastle said. But as they looked around at more navigational neurons, the team found that only a few fit into any predefined category.

"There were all these cell types that didn't have a name," Hardcastle said. "They weren't grid or border, head-direction or speed cells, which are the four main types. This started as an extension of previous work, but then it really took a left turn."

Most of the neurons they came across encoded a mix of navigational variables. For example, most neurons that appeared to be grid cells or head-direction cells also tracked speed. Speed cells, meanwhile, were tuned in strange ways. For example, one might fire when a mouse moved either quickly or slowly, but not at intermediate speeds.

And above all, it was hard to identify any particular set of neuron types, let alone a set that looked like standard navigational instruments. Instead, each neuron seemed to respond a little differently from each other.

"We didn't see grid cells or speed cells or head-direction cells," said Ganguli. "We saw this big continuum."

How the brain thinks

Giocomo said one of the take-home messages of this work is that there isn't a good mathematical model for the brain's navigation system. Existing models make assumptions that simply are not compatible with their results. "We need to rethink basically what the mechanism is."

There's a broader issue, too, Ganguli said: The cells of the brain do not necessarily think the way we think, in which case it could be misguided to assume the brain navigates using the same tools — speedometers, compasses, and so forth — as we would.

"The variables that the brain cares about may not be the same as the variables that the mind cares about. There may be a discrepancy between those. And if there is, then we somehow have to break free of the prejudices of our mind in order to understand the brain," Ganguli said.

Hardcastle is the Mark and Mary Stevens Interdisciplinary Graduate Fellow, affiliated with the Stanford Neurosciences Institute. Ganguli is also a member of Stanford Bio-X.

The work was funded by the New York Stem Cell Foundation, the James S. McDonnell Foundation, the Burroughs-Wellcome Trust, the Alfred P. Sloan Foundation, the McKnight Foundation, the Office of Naval Research the Stanford Center for Mind, Brain and Computation, and Bio-X. **ISM**

Closed-loop

continued from page 4

said, "When the system is in auto mode, it monitors my blood sugar every five minutes and keeps up the proper basal rate [of insulin]. Now I only have to check blood sugar four times a day. In the past, I had to check it a lot more, even up to 12 times a day."

Buckingham noted that the advance wouldn't be possible without the willingness of people like the Kurtzigs to participate in trials. "We have been very fortunate to have a diabetes community that's interested in doing studies and collaborating with us," he said.

Knowing that the device is not yet FDA-approved for children younger than 14, Sara Kurtzig is committed to the importance of participating in trials.

"We've had such a positive experience and have reached a new level of stability in Jamie's glucose control. So if we can play a part in making this technology available to all Type 1 diabetes patients, it feels like we are really making a difference," she said.

Jamie blogs about her experience and said the device has given her both freedom and responsibility she didn't have before.

"I do more things for myself now, but I still have to deliver insulin manually when I'm eating carbs because it doesn't do that on its own yet," Jamie said.

The Kurtzigs believe the improved control Jamie has seen with her closed-loop system has been worth the pricks, pokes and inconveniences that come with it.

"I wanted to sleep better and I wanted my mom to sleep better. I also really wanted to help other families and to contribute to science all around the world. Because of the trial, I really feel like I get to be a part of diabetes history," Jamie said.

Refining the systems

The goal of hybrid closed-loop systems is to make patients' diabetes care less of a burden and to keep their glucose values in a safe range so they can be healthier. To make further progress toward this goal, the Stanford team has been part of a multicenter, NIH-funded study group that is trying to eliminate the need for patients to give themselves an insulin dose (or bolus, as it is known in the diabetes world) before eating — an onerous task, particularly when it has to be done at every snack and every meal.

"In today's closed-loop systems, the insulin comes on a little slower and lasts a little longer than we would like," said Buckingham. "Those lag times make it difficult to provide insulin delivery for a meal in a full closed-loop system. We are looking forward to working with fast-acting insulins — and more rapid delivery — to improve meal glucose control and decrease the daytime burden of diabetes."

Stanford is the only institution involved in four National Institute of Diabetes and Digestive and Kidney Diseases research projects, which begin in the 2017-18 fiscal year. The projects will test multiple automated, closed-loop devices in what could be the final steps before requesting regulatory approval for permanent use.

Korey Hood, PhD, professor of pediatrics and of psychiatry and behavioral sciences at the School of Medicine, will lead the pediatric diabetes psychology research team that is investigating how to best help children and their families use these systems, and is partnering with Buckingham on the research.

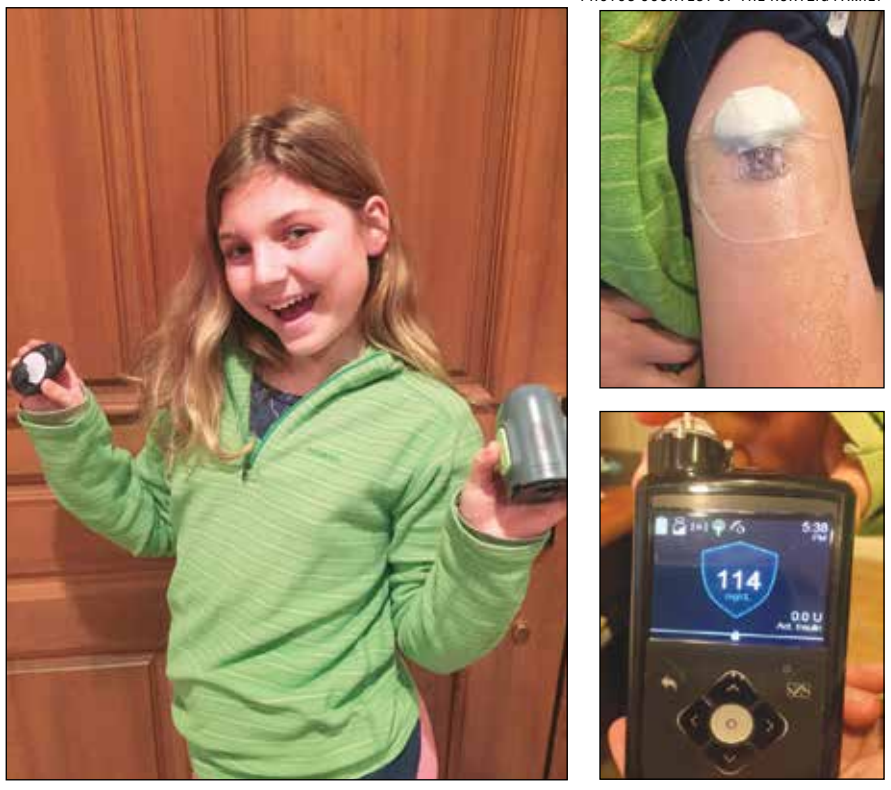
Improving a child's quality of life

"Part of our mission is to ensure that the system will be used properly by young patients, meaning that it has the desired impact on both a patient's health and quality of life," Hood said. "To that end, we evaluate the user experience by administering surveys and focus groups, and then we use those responses to generate new strategies and solutions to help the closed-loop system user."

Because the pancreas controls glucose both by releasing insulin to lower glucose levels and by releasing glucagon to raise glucose levels, another approach to closed-loop control is to give both insulin and glucagon. Stanford has participated in an NIH-funded, multicenter study that is testing the "bionic pancreas" developed at Boston University. This system has the potential to eliminate the need for carbohydrate counting before meals while also preventing hypoglycemia through the provision of glucagon. *The Lancet* recently published an article on this study.

David Maahs, MD, the new division chief of pediatric endocrinology at Packard Children's, said the program will continue "paving the way for better care, not just for our patients at Packard Children's, but for people with Type 1 diabetes everywhere." **ISM**

PHOTOS COURTESY OF THE KURTZIG FAMILY



(Left): Jamie Kurtzig, 12, holding some of her hybrid closed-loop system equipment. (Top right): The sensor inserted into Jamie's arm monitors her glucose levels and communicates the data to her insulin pump. (Bottom right): Jamie's MiniMed 670G insulin pump.

Krasnow

continued from page 1

one type of breathing: sighing. Knocking out these neurons eliminated sighing but left other modes of breathing unaffected. The discovery was published in *Nature* in 2016.

Krasnow and Yackle then set out to discover the respiratory role of another subpopulation of about 175 preBötC neurons distinguished by their shared expression of two genetic markers called Cdh9 and Dbx1. They bioengineered mice in which they could wipe out, at will, the neurons bearing both of these markers.

But once these rodents had their Cdh9/Dbx1 neurons eliminated, they seemed to take the loss in stride. Unlike their sigh-deprived brethren, there was no lacuna in these mice's portfolio of breathing variations.

Kevin Yackle

"I was initially disappointed," said Yackle.

But a few days afterward, he noticed something: For mice, the animals were extraordinarily calm.

"If you put them in a novel environment, which normally stimulates lots of sniffing and exploration," Yackle said, "they would just sit around grooming themselves" — evidence of what passes for mellowness when you're a mouse.

Further analysis showed that while these mice still displayed the full palette of breathing varieties from sighs to sniffs, the relative proportions of those varieties had changed. There were fewer fast "active" and faster "sniffing" breaths, and more slow breaths associated with chilling out.

Neurons as spies

The investigators surmised that rather than regulating breathing, these neurons were spying on it instead and reporting their finding to another structure in the brainstem.

This structure, the locus coeruleus, sends projections to practically every part of the brain and drives arousal: waking us from sleep, maintaining our alertness and, if excessive, triggering anxiety and distress.

It's known that neurons in the locus coeruleus exhibit rhythmic behavior whose timing is correlated with that of breathing.

In a series of experiments, the Stanford researchers proved that the preBötC neurons that express Cadh9 and Dbx1 not only project to the locus coeruleus — a new finding — but activate its long-distance projections, promoting brain-wide arousal.

"If something's impairing or accelerating your breathing, you need to know right away," said Krasnow. "These 175 neurons, which tell the rest of the brain what's going on, are absolutely critical,"

"The preBötC now appears to play a key role in the effects of breathing on arousal and emotion, such as seen during meditation," said Feldman. "We're hopeful that understanding this center's function will lead to therapies for stress, depression and other negative emotions."

Other Stanford co-authors are John Huguenard, PhD, professor of neurology and neurological sciences; Liqun Luo, PhD, professor of biology and an HHMI investigator; former postdoctoral scholar Lindsay Schwarz, PhD; and graduate student Jordan Sorkin.

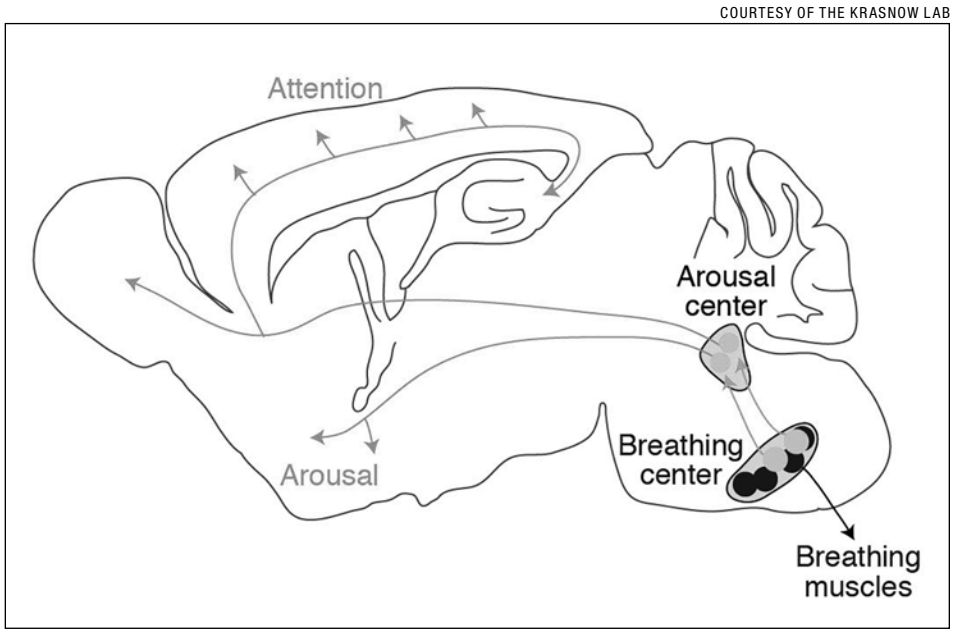
A researcher at the Chicago Medical School also co-authored the study.

Krasnow is also executive director of the Wall Center for Pulmonary Vascular Disease, a member of the Stanford's Neurosciences Institute, Cardiovascular Institute, Cancer Institute and Bio-X.

The study was funded by the National Institutes of Health and HHMI.

Stanford's Department of Biochemistry also supported the work. **ISM**

COURTESY OF THE KRASNOW LAB



The diagram depicts the pathway that directly connects the brain's breathing center to the arousal center and the rest of the brain.

Brunet

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was published online April 5 in *Nature*. Graduate student Shuo Han is the lead author.

The researchers began their study as a way to explore epigenetics, a process by which organisms modulate their gene expression in response to environmental cues without changing the underlying sequence of their DNA. In this case, the researchers were looking at how epigenetic protein complexes, which add or remove chemical tags on the cell's DNA packaging machinery, might interact with metabolic changes in a roundworm to affect its life span.

Understanding the link

"It's well-known that epigenetic protein complexes and metabolic pathways both affect life span in many animals," said Brunet, who also holds the Michele and Timothy Barakett Endowed Professorship. "But until now we didn't know why, or whether these two processes were linked in some way."

Han and Brunet set out to examine the effect of blocking the activity of a complex of proteins called COMPASS on the metabolism of laboratory roundworms. Roundworms are a popular animal model for longevity studies because of their relatively short life span and ease of care. Together, the COMPASS proteins add chemical tags called methyl groups to a component of a cell's DNA packaging machinery called a histone. The presence or absence of this tag affects whether the DNA remains wound up tightly like thread on a spool, or unfurls to allow its genes to be expressed.

> "We expected the long-lived animals in our study would be thinner. Instead, they turned out to be fatter."

Reducing the number of methyl tags on the histone keeps the DNA inaccessible, and researchers in Brunet's lab had previously shown that worms lacking COMPASS activity lived about 30 percent longer than their peers. Han wanted to know why.

"We thought that this epigenetic modification caused by COMPASS might mimic dietary restriction," Brunet said. "So we began looking at the metabolism and fat content of the worms lacking COMPASS activity."

Han noted that the worms lacking a functional COMPASS complex not only lived longer than their peers, but they also accumulated fats in their guts. Closer inspection with an analytical technique called gas chromatography coupled with mass spectrometry showed that the fat was primarily a specific class called monounsaturated fatty acids — the same kind of fat that's found in olive oil, nuts and avocados.

"This was exciting, but understanding why this was happening took some time," said Brunet. That's because COMPASS acts primarily in germline tissue, which makes the eggs and sperm. But the fat Han observed was accumulating in the intestine.

Inhibiting COMPASS

Han found that inhibiting COMPASS activity in the germline somehow caused a specific increase in the expression of enzymes that convert polyunsaturated fats into monounsaturated fats in the animals' guts. Although the method of communication between the germline and intestinal tissue is still under investigation, the finding was intriguing. Humans with diets rich in monounsaturated fats have been shown to have a reduced risk for heart disease and diabetes, and some studies have shown that centenarians store more monounsaturated fat than non-centenarians.

"We wanted to know whether this accumulation of monounsaturated fats was important to life span," Brunet said, "so we fed both monounsaturated and polyunsaturated fats directly to the worms. We found that the monounsaturated fats accumulated in the worms' guts and increased their life span even when COMPASS was not mutated. In contrast, polyunsaturated fats did not have the same effect."

The researchers are now working to understand how the monounsaturated fatty acid accumulation might work to extend life span. Some possibilities include the ready availability of quick energy in the stored fat, or the fact that the fat may provide an accessible source of lipid-based signaling molecules to facilitate communication between cells or tissues. Alternatively, the monounsaturated fats may help preserve the fluidity of the lipid membranes that enclose and protect cells.

Brunet is a member of Stanford's Cardiovascular Institute, Cancer Institute, Neurosciences Institute and BioX.

Other Stanford co-authors of the paper are former postdoctoral scholars Elizabeth Schroeder, PhD, and Katja Hebestreit, PhD. Researchers from Harvard also co-authored the study.

The research was supported by the National Institutes of Health, the National Science Foundation and Stanford Mass Spectrometry. The Department of Genetics also supported the work. **ISM**

Two faculty members named Outstanding Investigators by National Cancer Institute

By Krista Conger

The National Cancer Institute has named professor of dermatology Howard Chang, MD, PhD, and professor of oncology Ronald Levy, MD, as recipients of the institute's Outstanding Investigator Awards for 2016.

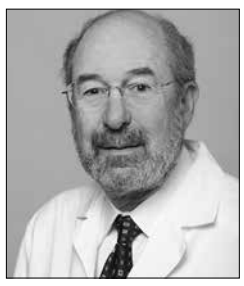
Howard Chang

The awards provide funding to investigators with outstanding records of productivity in cancer research. Recipients receive up to $600,000 each year for seven years to pursue or extend research projects of unusual potential.

"This is a great honor and I am delighted to have this opportunity," said Chang. "We plan to use this award to investigate how a class of genes called long noncoding RNAs are involved in human cancers. We are particularly interested in how long noncoding RNAs may make each cell within the cancer different from one another — a property that makes cancer difficult to treat — and also how specific chemical changes alter the meaning of long noncoding RNAs in cancer."

Levy is investigating ways to train the immune system to attack and eradicate cancer cells.

"We are combining the discoveries that stimulate the immune system with new knowledge about the Achilles' heels of cancer cells," said Levy, who is the Robert K. and Helen K. Summy Professor in the School of Medicine. "Great strides have been made in these fields and we hope to bring them together to help patients."



Ronald Levy

"The NCI Outstanding Investigator Award addresses a problem that many cancer researchers experience: finding a balance between focusing on their science while ensuring that they will have funds to continue their research in the future," said Dinah Singer, PhD, director of NCI's Division of Cancer Biology. She added that providing seven years of uninterrupted funding gives investigators the opportunity to fully develop ambitious cancer research programs.

Chang is a member of Stanford's Child Health Research Institute, Cancer Institute, Neurosciences Institute, ChEM-H and Bio-X. Levy is a member of the Stanford Cancer Institute and Bio-X. **ISM**

Random Acts of Flowers delivers smiles, warmth to Stanford Hospital patients

By Jana Chow

When Camille Kennedy enters patient rooms at Stanford Health Care, she is reminded of the isolation she felt when she was admitted to the hospital after an unexpected trip to the Emergency Department.

"When you end up in the hospital, you may find yourself in a place you did not plan to be," she said. "You think your life is going one way, and it takes a turn."

These days, Kennedy uses her experience as a patient as motivation to help break through the isolation other patients experience. Kennedy is executive director for Random Acts of Flowers Silicon Valley, an organization that delivers recycled flowers and encouragement to Stanford hospital patients each month, and to patients at hospitals and health care facilities throughout the Bay Area.

Random Acts of Flowers collects unused flowers from florists, grocery stores and flower markets throughout the Bay Area. Volunteers assemble all the flowers into new bouquets, then hand deliver them to patients.

"We are upcycling," Kennedy said. "Each week, we typically end up with between 4,000 and 8,000 stems of flowers. We use these to create hundreds of bouquets. Most flowers perk up, and we compost anything we don't use."

NORBERT VON DER GROEBEN

Volunteers Sandra Bachman (left) and Patricia Hartnell make deliveries to patients at Stanford Hospital as part of Random Acts of Flowers Silicon Valley.

A human connection

While the flowers provide a tangible gift for volunteers to give to patients, Kennedy feels the real value of Random Acts of Flowers is that it delivers a human connection to lonely patients.

"We are trying to combat isolation, and bring people together physically — not just digitally," she said. "Our volunteers talk with patients, give a handshake or a hug, and always a smile. That interaction and endorphin boost is really terrific for both the patient and the volunteer."

Many of these volunteers have personal experience with being a patient, and have found healing through helping other patients.

Between 2009 and 2010, Sandra Bachman spent four months in and out of Stanford Hospital. These were the hardest and scariest days of her life, she said, and she now credits the hospital and staff for saving her life. Volunteering with Random Acts of Flowers has given her an opportunity to redeem her experience at the hospital and to give back.

"The first time I volunteered here, I held my breath as I walked into the hospital," she said. "I was anxious, and the trauma of my hospital stay came back. I had to build up courage before I delivered flowers to each patient."

By the end of that day, she had created positive memories in a place that had previously filled her with fear. She now looks forward to volunteering with Random Acts of Flowers at Stanford Hospital each month.

"Doing this has been incredible for me," she said. "When patients smile, it makes their families and friends smile, and it makes me smile. It's amazing how contagious it is. I get goosebumps every time." ISM

CME center launches webinar series for health professionals on hot topics in medicine

By Ruthann Richter

Stanford Medicine's Center for Continuing Medical Education is launching a series of free webinars on hot topics in medicine, featuring Stanford experts who will provide guidance to physicians and other health professionals on controversial and challenging issues they may face in their practices.

The first webinar, to be offered May 16, will feature two Stanford specialists in pediatric infectious disease who will discuss challenges of dealing with Zika virus. They will offer physicians advice on management and prevention of Zika infection, which can cause serious neurological complications in infants born to infected women. The webinar comes at the start of the warm season, particularly in the southern part of the country, when Zika-carrying mosquitoes are more active and a resurgence of the disease may occur.

The webinar will feature Desiree LaBeaud, MD, an associate professor of pediatrics whose research focuses on Zika and other mosquito-borne infections. The one-hour session will be moderated by Charles Prober, MD, professor of pediatrics and senior associate dean for medical education at the School of Medicine.

It will be the first in a series of webinars this year, all designed to showcase Stanford's expertise on timely issues of pressing concern to physicians and other providers, said Linda Baer, the school's director of CME.

"What we are trying to accomplish through this new series is having our Stanford experts seen on a national stage for the excellent research and clinical work we do here, and to get doctors up to speed on difficult issues they may face in their day-to-day practices," Baer said.

The first webinar is designed for primary care physicians, pediatricians, neurologists, infectious disease specialists and obstetrician/gynecologists, as well as nurse practitioners and physician assistants.

Baer said future webinar topics have yet to be finalized, though they could deal with such issues as physician-assisted suicide, medical marijuana and opioid use and addiction.

The course will be valid for 1.0 CME credit. Interested clinicians can sign up for the first webinar at: https://med.stanford.edu/cme/courses/online/webinars/zika_news.html. ISM

Moore

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after a child in their family benefited from the care of the Children's Heart Center. "Our grandchild had lifesaving surgery at the hospital, and we would like to help make sure the capability is there for others," Gordon Moore said.

"We are honored to have the Moores' visionary partnership as we strive every day to heal humanity through science and compassion, one child and family at a time," said Christopher Dawes, president and CEO of Lucile Packard Children's Hospital Stanford. "The Betty Irene Moore Children's Heart Center will provide world-leading cardiac care to patients today, tomorrow and for generations to come."

Next wave of innovation and discovery

Over the past 70 years, new surgical techniques and medical therapies, some of which were developed at the Stanford School of Medicine and Packard Children's, have evolved and greatly improved outcomes for children with almost every type of congenital heart disease.

Heart defects that were once universally fatal can now be surgically improved. As patients born with heart disease survive longer, there are now more adults than children in the United States with congenital heart disease. However, further advancements are still needed to ensure a healthier future for patients, many of whom continue to face a compromised quality of life and require subsequent surgeries.

"Surgical intervention can repair, but it rarely can truly cure," said pediatric heart surgeon Frank Hanley, MD, who is also the Lawrence Crowley, MD, Endowed Professor in Child Health at the School of Medicine and executive director of the Betty Irene Moore Children's Heart Center.

"Children who have received complex surgical intervention to repair a cardiac abnormality require careful monitoring and specialized care throughout their life span," Hanley added. "We imagine a day when a child born with a poorly working aortic valve, rather than undergoing multiple open-heart operations throughout his lifetime, instead receives a replacement valve engineered from his own stem cells. Dr. and Mrs. Moore's gift comes at a critical juncture — enabling us to advance beyond surgical repair to the discovery of transformational treatments and interventions and, ultimately, to true cures."

The center has an overall survival rate of 98 percent. Beyond survival alone, the goal is now to ensure an excellent overall outcome — from normal brain function for even the most fragile patients, to the ability for children to perform well in school and to exercise and enjoy an active life into adulthood.

Lifetime of care

"We are committed to providing babies and children with heart disease and their families with the happiest, healthiest lives possible, from the early identification of problems, to expert intervention, and finally to a lifetime of care and support," said Stephen Roth, MD, MPH, chief of pediatric cardiology and director of the Betty Irene Moore Children's Heart Center.

"Dr. and Mrs. Moore's incredible gift will not only bolster our clinical capabilities for children and families receiving care now in the Betty Irene Moore Children's Heart Center, it will also accelerate basic and translational research by Stanford Medicine faculty and scientists to develop more precise techniques to predict, prevent and cure," said Lloyd Minor, MD, dean of the School of Medicine. "When it comes to achieving precision health, we must think as big as we can — not just about treating disease, but about making and keeping people healthy — and nowhere is this more true than in children."

In 2017, Packard Children's will complete its major expansion, becoming the most technologically advanced, family-friendly and environmentally sustainable children's hospital in the nation. The Moores' gift will enable the Children's Heart Center to expand its state-of-the-art clinical and research facilities, train the future leaders of cardiovascular medicine and surgery, and improve the field of pediatric cardiology and pediatric cardiovascular surgery through innovative research.

In addition, the center will expand its clinical facilities, including a newly designed outpatient center.

Packard Children's established the Children's Heart Center in 2001 to focus more expertise and resources on congenital heart disease, the most common type of birth defect worldwide. Each year, approximately 40,000 children in the United States are born with heart defects, and an additional 25,000 children develop some kind of acquired heart disease.

The center has gained recognition as a national and international destination program for several highly specialized surgical procedures, and is also a full-service cardiology program that cares for patients with all forms of cardiovascular conditions.

Under the leadership of Hanley and Roth, the center receives more than 25,000 patient visits annually and performs 80 to 90 percent of all cardiac surgical care for children in northern and central California. ISM

David Schneider appointed chair of microbiology and immunology

By Bruce Goldman

David Schneider, PhD, has been appointed chair of the School of Medicine's Department of Microbiology and Immunology. His five-year term began April 1.

"This world-class department has seeded a good deal more than its fair share of academic scientists studying microbial pathogenesis and immunology," said Schneider, professor of microbiology and immunology. "I hope to nourish this culture and teach it to our students and postdocs so that we can sustain the innovation and leadership our pioneering faculty has demonstrated."

Schneider's current research focuses on quantitative analysis of sickness during infections and, in particular, on determining how we recover from infections. He has spent the last several years investigating the fundamental causes of resilience to infection and developing mathematical models to predict recovery and well-being after infection.

"Dr. Schneider is a brilliant innovator and respected educator and mentor," said Lloyd Minor, MD, dean of the School of Medicine. "I am thrilled that he will bring his experience and perspective to this role."

David Schneider

Schneider replaces Peter Sarnow, PhD, who has chaired the department since 2010. "Dr. Sarnow brought superb scientific and leadership acumen to the department, advancing cutting-edge research, supporting and developing faculty, and assisting postdoctoral scholars in finding success in academia and industry," Minor said.

Schneider received his BS in biochemistry from the University of Toronto in 1986 and earned a PhD in molecular biology at the University of California-Berkeley in 1992. He first came to Stanford as a postdoctoral scholar in 1996, between postdoctoral appointments at UCB and UCSF. Between 1997 and 2001, Schneider was a Whitehead Fellow at the Whitehead Institute in Cambridge, Massachussetts. He returned to Stanford as an assistant professor in 2001, was promoted to associate professor in 2008 and became a full professor this year. He is a member of Stanford Bio-X and the Stanford Child Health Research Institute.

Founded nearly 100 years ago, the Department of Microbiology and Immunology numbers more than 25 faculty, 100 postdoctoral scholars and 50 graduate students in addition to about two dozen research, administrative and support staff.

"I see our department, and Stanford in general, as a place where we aren't pigeonholed as being certain sorts of scientists," said Schneider. "When we come up with new ideas, our colleagues don't say, 'What do you know about that?' Rather, they share your excitement and urge you on." ISM

OF NOTE

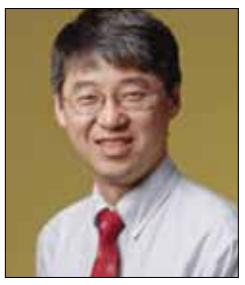
reports on significant honors and awards for faculty, staff and students

Daniel Chang

Chitra Dinakar

Louanne Hudgins

Michelle James



David Liang

Geoffrey Lighthall

Michael Longaker

Sergiu Pasca

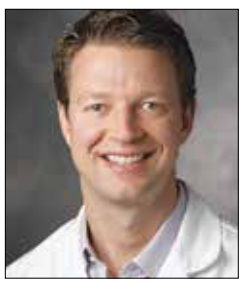
VJ Periyakoil

Maria Polyakova

James Priest

Maria Grazia Roncarolo

Manish Saggar



Thomas Weiser

DANIEL CHANG, MD, was promoted to professor of radiation oncology, effective March 1. His clinical focus is on gastrointestinal malignancies, and his research interests include developing stereotactic body radiotherapies for liver tumors and the use of functional imaging to gauge treatment response.

CHITRA DINAKAR, MD, clinical professor of medicine, will serve as an at-large representative on the board of directors of the American Academy of Allergy, Asthma and Immunology. Her term runs from 2017 to 2021. Her research and clinical interests include asthma, food allergies, therapy adherence, and health care disparities and outcomes.

LOUANNE HUDGINS, MD, professor of pediatrics, was named president of the American College of Medical Genetics and Genomics. Her two-year term began April 1. Hudgins is also the medical director of Stanford's master's program in human genetics and genetic counseling, the director of perinatal genetics and the medical director of the clinical genomics service at Stanford Children's Health.

MICHELLE JAMES, PhD, was appointed assistant professor of radiology and of neurology and neurological sciences, effective March 1. Her research focuses on developing and evaluating molecular imaging agents to improve the detection and treatment of brain diseases, particularly Alzheimer's disease.

DAVID LIANG, MD, PhD, was promoted to professor of medicine, effective March 1. His clinical focus is on Marfan syndrome and other aortic diseases. His research focuses on cardiac imaging, particularly image guidance of procedures.

GEOFFREY LIGHTHALL, MD, PhD, was promoted to professor of anesthesiology, perioperative and pain medicine, effective March 1. His interests include the evaluation and stabilization of critically ill patients outside of the ICU and the use of patient simulation as an educational and training tool.

MICHAEL LONGAKER, MD, the Deane P. and Louise Mitchell Professor and a professor of surgery, is part of a consortium that has received $12 million in funding over three years from the National Institute of Dental and Craniofacial Research to investigate dental, oral and craniofacial tissue regeneration. The funding will support a new California-based project called the Center for Dental, Oral, and Craniofacial Tissue and Organ Regeneration. C-DOCTOR will focus on facilitating tissue-regeneration clinical trials.

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, has received the 2017 Jordi Folch-Pi Award from the American Society for Neurochemistry. The honor recognizes a young investigator who has significantly contributed to the understanding of neurochemistry and has a high potential for future accomplishments. The award includes a $1,500 prize and was presented this month at the ASN meeting in Arkansas. Pasca's focus is on generating 3-D brain models from stem cells to understand development and capture mechanisms of disease.

VJ PERIYAKOIL, MD, was appointed associate professor of medicine, effective March 1. She directs Stanford Palliative Care Education Training and is the associate director of palliative care services at the VA Palo Alto Health Care System. She is the founder of the Letter Project, an effort to promote advance-care planning.

MARIA POLYAKOVA, PhD, assistant professor of health research and policy, has received one of two 2017 Distinguished CESifo Affiliate Awards in applied microeconomics from the CESifo Group in Germany. The award is given to independent investigators within the first five years of their PhD. Polyakova was honored for her work on consumer choices in insurance markets.

JAMES PRIEST, MD, was appointed assistant professor of pediatrics, effective March 1. His focus is on understanding the genetics and pathogenesis of congenital heart disease using translational genomics, big data and vertebrate models of cardiac development.

MARIA GRAZIA RONCAROLO, MD, professor of pediatrics and of medicine, chief of pediatric stem cell transplantation and regenerative medicine, and co-director of the Bass Center for Childhood Cancer and Blood Diseases, will receive the 2017 Outstanding Achievement Award from the American Society of Gene and Cell Therapy, the society's highest honor. Roncarolo is being recognized for her contributions to the field of gene and cell therapy. She will accept the award in May in Washington, D.C., at the organization's annual meeting.

MANISH SAGGAR, PhD, was appointed assistant professor (research) of psychiatry and behavioral sciences, effective March 1. He is also a faculty member at Stanford's Hasso Plattner Institute of Design, or d.school. He is a computational neuroscientist who examines brain dynamics at rest and during learning.

THOMAS WEISER, MD, was promoted to associate professor of surgery, effective March 1. He is a general and trauma surgeon and a surgical intensivist. Weiser's research focuses on evaluating postoperative outcomes and barriers to surgical access in resource-poor settings and on developing interventions to improve safety and reliability of care. ISM