New med students arrive from near and far

By Mandy Erickson

Wearing a red dress, a basket cap, abalone shell earrings and a mink pelt, Melissa Eidman strode up to the microphone during the School of Medicine’s white coat ceremony and announced her home town: Weitchpec, California.

Weitchpec, in the state’s far northwestern corner, is the home of her ancestors, the Yurok Tribe. Her accessories are traditional garb: the pelt is a family heirloom. Eidman grew up in Sacramento, but once she’s a fully trained physician, she plans to return to the Yurok reservation to care for its residents.

“T’m excited and honored to be wearing it,” Eidman said of the white coat, which had her name embroidered on it. The coat is new, but for Eidman, Stanford isn’t: She transferred as an undergraduate after spending years at a community college. “It’s been quite a long haul,” she said.

Ninety medical students donned white coats at the Aug. 23 ceremony outside the Li Ka Shing Center for Learning and Knowledge. In a separate ceremony earlier that afternoon, 28 news students of the physician assistant program also put on white coats. The events marked the beginning of the students’ respective programs.

All students also received stethoscopes, gifts from the Stanford Medicine Alumni Association.

Diverse class

“By all accounts, you are among the most accomplished people on the planet,” Dean Lloyd Minor, MD, told the new medical students at their ceremony. “When you receive your coat and stethoscope, you’re showing your willingness to run toward crises and not away from them.”

The medical students hail from New York; Houston; and nearby Redwood City, California, as well as from Kazakhstan, Venezuela and England, among other places. The class of 2023 is among the most diverse in Stanford’s history, with 26% who identify as an ethnicity under-represented in medicine, 34% who were born outside the United States and 8% who are LGBTQ.

Many students said they would need to get used to wearing the white coat. “It feels really surreal,” said Bithal Elakh, a medical student from Sudan and Chicago. “It’s something I’ve aspired to since high school.”

“The idea of being a medical student has been abstract for a long time,” said Samson Peter of San Mateo, California. “But this coat makes it all very tangible.”

They also felt the burden of responsibility that the white coat carries — “an overwhelming sense of accountability,” said Alexander Samson.

Infammation may trigger silent mutation, causing deadly lung disease, study shows

By Tracie White

Researchers at the School of Medicine have found that inflammation in the lungs of rats, triggered by something as simple as the flu, may wake up a silent genetic defect that causes sudden onset cases of pulmonary hypertension, a deadly form of high blood pressure in the lungs.

“T’s a kind of one-two punch,” said Amy Tian, PhD, senior research scientist in pulmonary and critical care. “Basically, the first hit is the mutation, and the second hit is inflammation in the arteries of the lungs. You can be healthy and carrying this mutation, and all of the sudden you get a bacterial or viral infection, and it leads to this terrible disease.”

Tian is the lead author of the study, which was published Aug. 29 in Circulation. Mark Nicolls, MD, professor and chief of pulmonary and critical care medicine, is the senior author.

“This is important research for understanding how ‘second hits’ can render ordinarily silent genetic mutations deadly,” Nicolls said. “It also furthers the scientific understanding of the role of inflammation in pulmonary hypertension.”

There is no known cause of pulmonary hypertension, a debilitating disease that causes difficulty breathing, fatigue and chest pain. It can leave patients too weakened to perform simple daily activities, such as climbing a flight of stairs. About 200,000 people a year are hospitalized with the disease in the United States, according to the Pulmonary Hypertension Association of America. The only available cure for severe forms of the disease is lung transplantation, but it has only a 30% survival rate.

Response to flu vaccine affected by gut bacteria, according to scientists

By Bruce Goldman

A new study in healthy adults suggests that antibiotics may reduce the effectiveness of the flu vaccine.

The depletion of gut bacteria by antibiotics appears to leave the immune system less able to respond to new challenges, such as exposure to previously unencountered germs or vaccines, said Bali Pulendran, PhD, professor of pathology and of microbiology and immunology at the School of Medicine.

“To our knowledge, this is the first demonstration of the effects of antibiotics on the immune response in humans — in this case, our response to vaccination — directly induced through the disturbance of our gut bacteria,” he said.

The study was published Sept. 5 in Cell. Pulendran, who holds the Violetta Bali Pulendran.

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Researchers enhance neuron recovery in rats after blood flow stalls

By Jonathan Wosen

Researchers at the School of Medicine report in a new study that they found a way to help rats recover neurons in the brain’s center of learning and memory. They accomplished the feat by blocking a molecule that controls how efficiently genetic instructions are used to build proteins.

If the approach described in the study could be applied to humans, it may one day help patients who’ve suffered a stroke, cardiac arrest or major blood loss and are thus at higher risk of memory loss.

In the study, published online Aug. 19 in the journal *eNeuro*, scientists induced extremely low blood pressure — as would happen when the heart stops beating — in rats. These rats lost neurons in a specific region of the hippocampus critical to learning and memory, but the researchers improved the animal’s recovery by injecting a molecule that blocks a microRNA: a short molecule that regulates gene expression by preventing the conversion of genetic blueprints into proteins.

Scientists haven’t established whether a microRNA blockade potentially causes astrocytes — cells that support neurons and make up 50% of cells in the brain — to turn on neurons.

The findings demonstrate that neurons, with some assistance from their astrocyte neighbors, recover in a region of the hippocampus not known to have a local stem cell population that can replenish lost neurons. Enhancing this recovery in humans could help those who’ve suffered a temporary loss of blood flow to the brain.

“There’s currently no treatment to improve brain function in patients with heavy blood loss, cardiac arrest or stroke,” said Creed Stary, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine. “This is the first study to show that the normal process of post-traumatic hippocampal recovery can be substantially improved with a pharmacological microRNA-based therapy.”

Stary is the study’s senior author. Lead authorship is shared by postdoctoral scholar Brian Griffliths, PhD, and senior research scientist Yi-Bing Ouyang, PhD.

Under (low) blood pressure

When fresh blood stops flowing through the brain, cellular waste piles up, and neurons starved of oxygen and glucose eventually die. This can occur when a person has a stroke, loses a significant amount of blood or suffers a cardiac arrest.

Amid the damage, levels of a microRNA known as miR-181a surge in astrocytes. In an earlier study, the researchers blocked miR-181a with a molecule designed to stick to and inactivate the microRNA. They found that blocking the molecule reduced brain injury in rats of blood to the brains of rats stopped neurons from dying.

“If you want to find a therapy for an injury, one approach is to look for disruptions that occur in cells and try to reverse them. The first step was asking, ‘Is reversing the increase in this specific microRNA protective?’” Stary said.

But while the prior findings were encouraging, they didn’t reflect how such an intervention would probably be used in a clinical setting: it’s more likely that a patient would receive a microRNA blockade after an injury.

To test whether miR-181a blockade helped rats recover hippocampal neurons, the researchers decreased the rats’ blood pressure dramatically by siphoning off much of their blood and reinfusing it 10 minutes later. Similar drops in blood pressure can occur in people during cardiac arrest, after a major loss of blood or during certain surgeries.

The blood pressure drop caused nearly 95% of neurons in a region of the hippocampus known as CA1 to die off. By around two months after the procedure, those neurons bounced back to nearly 50% of normal levels.

The researchers then tested the effects of a microRNA blockade by injecting the blocking molecule directly into the hippocampus of rats either two hours or seven days after the procedure. These rats had significantly higher neuronal recovery than those injected with a control molecule that didn’t target any known microRNAs. In earlier studies, the researchers showed they could deliver the blockade intravenously, making it well-suited for clinical use.

Solving a puzzle

But the fact that there was any recovery was puzzling. The hippocampus is one of the few brain regions that harbors neural stem cells, which can form new neurons in adults, but not in the CA1 region the researchers were studying.

“If you don’t have new neural stem cells and you don’t have any evidence of cell division, then how are CA1 neurons being repopulated?” Stary said.

The researchers had one important clue: When CA1 neurons were at their nadir, specialized neuronal support cells, known as astrocytes, were at their highest levels in rats in which miR-181a had been blocked.

To find out what happens in the astrocytes when miR-181a is blocked, the researchers fixed astrocyte cells by injecting a molecule that blocks a microRNA: a short molecule that regulates gene expression by preventing the conversion of genetic blueprints into proteins.

Scientists then treated the cells by injecting the blocking molecule directly into the hippocampus of rats either two hours or seven days after the procedure. These rats had significantly higher neuronal recovery than those injected with a control molecule that didn’t target any known microRNAs. In earlier studies, the researchers showed they could deliver the blockade intravenously, making it well-suited for clinical use.

Almost 30 years after the launch of the International Human Genome Project, which aimed to map the human genome, many ethical, legal and social concerns surrounding genetic research, Cho noted. Yet there’s no central repository where people grappling with such issues can easily find ethical or policy guidance, or published research, or connect with experts who can help guide them.

“I think it should be easier for people who are writing legislation or trying to do with consumer genetic testing, or the release of data from Ancestry, to be able to understand knowledgeable about the implications of data collection by genomic companies,” said Mildred Cho, professor of pediatrics and of medicine.

Filling a void

“If the center is poised to fill that void with a new web portal for ELSI content that will be identified, collected and shared. Cho expects that content to come from such sources as scientific and academic research, narratives and commentary, scientific journals, laws and legal briefings.

Through such data collection, the center’s leaders hope to gain a better understanding of gaps in knowledge and information gaps among practicing ELSI researchers. They also hope to help influence scientific investigation by bringing together experts and by holding a separately funded biennial congress to bring them together.

But central to center’s aim is to share ELSI knowledge with people who might not be aware it’s available, and to tailor the information for specific stakeholders — policymakers, medical professionals, journalists and even scientists themselves. This is important, Cho said, because ELSI content draws from a number of disciplines, including philosophy, sociology, psychiatry, economics and politics.

“We’re going to try to develop new methods for synthesis.” — Mildred Cho

Mildred Cho to co-lead new coordinating hub for biomedical ethics

By Patricia Hannon

The Stanford Center for Biomedical Ethics has been chosen by the National Human Genome Research Institute to co-lead new coordinating hub for biomedical ethics.

The effort will be led by Mildred Cho, PhD, associate director of the Stanford Bio-X and the Wu Tsai Neurosciences Institute at Stanford. Other Stanford co-authors of the study are researchers associated Lijun Xu, MD, and Xiaoyun Sun, MD; and Rona Coffard, MD, PhD, professor of anesthesiology, perioperative and pain medicine.

This study was supported by the American Heart Association and the National Institutes of Health.

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“We’re going to try to develop new methods for synthesis.” — Mildred Cho
way for a new approach to biomolecular research: the analysis of real-world data. The term “real-world data” comes from the idea that EHRs aren’t just health histories of single individuals; they’re a trove of information that can help guide clinical decisions, from diagnosis to treatment.

In 2016, the 21st Century Cures Act became federal law. It helped bring about a new focus on harnessing real-world data in medicine, as opposed to letting clinical trials be the only way to get high-quality scientific data and also not as well. It turns out the accuracy of the prediction depends on how the data is gathered and organized.

Science writer Hanna Armaghian spoke with Hernandez-Boussard about the value of real-world data, how it fits into the current clinical care landscape and what her research revealed about harnessing this immense dataset.

What’s the most important contribution of real-world data to medical decision-making?

Hernandez-Boussard: It’s really the generalizability that’s traditionally been a major problem with clinical trials, which is a given problem that has a provided a real advantage. When we talk about the population that we’re representing, it’s a representative of the way most the population receives their care. Real-world data doesn’t have strict inclusion or exclusion criteria, so it means that any clinical assertions made with that data can apply to a typical patient seeking routine care.

Very often “gold standard” clinical trials are looking at a particular drug for a particular disease, and patients can end up excluded if they have conflicting comorbidities, some of which can be quite common. So, for example, we can’t find out if a cancer drug is effective in patients who have hypertension or diabetes. But in reality, the patients with hypertension and diabetes might be the ones who really benefit from the drug. And so looser inclusion and exclusion criteria enables us to see how this drug works, or doesn’t work, in much broader populations and subpopulations of patients.

Your team set up a case study to evaluate real-world data in the context of cardiovascular medicine. What did the study investigate and what were the most significant takeaways?

Hernandez-Boussard: With our case study, we set out to see whether real-world evidence could be used to guide clinical assertions, such as identifying a patient with a particular disease or guiding treatment options. It seems reasonable to expect that real-world data could help make those clinical assertions, but this data largely comes from electronic health records and insurance claims. They’re not intended to guide care for other patients, not. Even when researchers are interested in the larger population, they’re really complex and messy. So, any data we pull out of them has to be done with great caution. We wanted to assess how accurate the assertions made with that data can apply to a typical patient seeking routine care.

Note different diseases. We tend to think of this data as more regularly curated, and therefore more accurate, but our case study showed us that the most rich information is actually in the clinical narrative text, or unstructured data — for example, the free text notes that a clinician takes during a patient visit.

In our study we found that we were more accurately able to identify different aspects of the population — like diseases or procedures they’d had when using just the unstructured data. So for example, we wanted to see if we could identify the population of patients who had coronary artery disease. When we used structured data we were able to do that. So it might be that we use the unstructured data, that jumped up to 95%.

When we think about how clinicians and patients interact, the clinician is an active listener and note-taker, capturing much of their conversation in written narrative form. That’s where they’re likely able to provide the most details about the patient, as opposed to structured data, which fall under into the electronic health record category. So we end up getting richer, more accurate information when we just analyze free text.

What were the limitations of using real-world data in your case study?

Hernandez-Boussard: I would say that the technology to actually run the algorithms that harness real-world data is, in many ways, a limiting factor. For this study, we used state-of-the-art artificial intelligence technologies. And to be able to harness real-world data effectively is a key part, but no one has access to it or the expertise to conduct that kind of analysis. The second limitation is actually having access to data on a large scale while being compliant with privacy laws. While we were able to conduct our study with the data from Verantos, data studies also are a very real problem, and it’s not always easy to gain access to such a large amount of data that encompasses different health care settings from different geographical locations. These diverse datasets are important to address the generalizability of the technologies.

Why is there an increasing trend toward using real-world evidence instead of, or in conjunction with, the traditional clinical trial to inform medical decision-making?

Hernandez-Boussard: There are a handful of reasons. First, clinical trials are pricey — we’re talking millions and millions of dollars — and they only encompass a very small portion of the population. Real-world data repurposes EHRs to guide clinical care at a fraction of the cost. The second is the lack of certainty about real-world data is more that they’re not often broadly generalizable. The patients that are included in trials often do not fully represent the range of patients that could benefit from a new drug or therapy. Third, these clinical trials are highly controlled. Patients come in for an appointment or treatment and in, say, a few weeks until they schedule their next appointment. They might be on vacation and need to wait three weeks until they schedule their next appointment.

How do you think real-world evidence can best fit into a clinical care setting?

Hernandez-Boussard: Clinical trial data still provides the highest level of certainty for guiding clinical care. But if, for example, you run a clinical trial, and end up with a very specific subpopulation, how would you know how well that drug works in that subpopulation? And that’s where we think real-world data could fill in a gap.

We’re not suggesting that real-world evidence should replace clinical trials by any means — clinical trials are still held in high regard. Instead, it’s something of a hybrid situation, with patient benefitting from both sides.

Applications for Chan Zuckerberg Biohub fellowships open to residents, clinical fellows

The Chan Zuckerberg Biohub, a medical research organization that collaborates with Stanford, UC-Berkeley and UC-San Francisco, is accepting applications for one-year research fellowships for medical residents and clinical fellows. The fellowship program allows fellows to conduct research under a faculty mentor at one of the three campuses or at a Chan Zuckerberg Biohub lab in San Francisco. Fellows will also learn about biomedical, clinical and ethical regulations.

The goal of the fellowship is to equip young doctors to incorporate research into their careers. The number of physician-scientists is in decline, largely because of financial pressures on academic medical centers.

“Despite their important role in biomedical discovery, fewer physicians are dedicating their professional lives to research,” said David Cornfield, MD, the program’s co-director and a professor of pediatrics at the Stanford School of Medicine. “The CZ Biohub Physician-Scientist Fellowship Program aims to change that by providing medical doctors who have limited research experience with the opportunity to pursue a basic research career in medicine and cultivate their passion for advancing medical knowledge."

The program will award about six fellowships per year. Applicants must hold an MD degree but not a PhD, and be enrolled full-time in a medical residency or clinical fellowship at Stanford or UCSC. They will need to commit to at least two years at 75% time with CZ Biohub and spend at least 20% of their time seeing patients. The fellowship will begin July 1, 2020.

The Biohub is accepting applications until Oct. 1, 2019; awards will be announced in December. Fellows can expect to be paid a salary similar to the one they are receiving for their residency or current position. Applicants can find more information and apply at https://www.czbiohub.org/fspm.

Ethics

Ethics continued from page 2

sizing different kinds of knowledge that typically aren’t combined,” Cho said.

The center’s call for a wealth of expertise to the project led to an opportunity for a research scholar at Stanford’s C e n t r e for Biomedical Ethics, and other Columbia faculty members who specialize in ethics, genetics and biomedical informatics will work at their campus to build the ELSI community. They will also partner with Columbia’s Graduate School of Journalism to assess how journal-”

"We have the opportunity to have our fingers on the pulse of ELSI research."

“We have the opportunity to have our pulses on the ELSI research and understand where the field is going and where it needs to go,” Cho said.

Cho also leads the Center for Integration of Research on Genetics and Ethics at Stanford. It was estab-lished in 2004 as one of several Hu-man Genome Research Institute’s Centers for Excellence in ELSI research and is based at Stanford’s Center for Biomedical Ethics. 3
New adult hospital to host community open house Sept. 14-15

The new Stanford Hospital will officially open its doors to patients in the fall, but on Sept. 14 and 15, local residents can get a sneak peek as part of a two-day community open house featuring a multimedia experience and a health- and wellness-inspired street fair with food trucks and family activities.

“We are thrilled that our vision of expanding our world-class academic medical center has come to fruition,” said David Entwistle, president and CEO of Stanford Health Care. “The new Stanford Hospital is first and foremost our community’s hospital.”

Open house visitors will be able to take part in a 50-minute multimedia experience of the new facility. They’ll have the opportunity to learn about the robots that deliver supplies throughout the building, the technology-rich patient rooms and operating suites, the safety features, original art and rooftop gardens. Experts also will be on hand to answer questions about the building’s design and construction and the advanced patient care technologies.

“The community open house events will be a once-in-a-lifetime opportunity for the general public to go behind the scenes of the new hospital before it opens,” said Maggie Pringle Grauer, chair of the Stanford Medicine Community Council. “We are creating an experimental tour that will give visitors a firsthand look at the delivery of modern medicine.”

In the promenade between the original Stanford Hospital and the new building, there will be a street fair with interactive activities for all ages. Booths will feature demonstrations of the latest telehealth and virtual reality tools used in surgery and patient care. There also will be health and nutrition advice, a larger-than-life game of Operation, Stanford’s therapy dogs, face painting, a treasure hunt, balloons, live music and a teddy bear triage area, where kids can care for the stuffed animals and take them home.

Visitors will also have the chance to view the Stanford VOICES digital mural project, a mosaic of more than 4,000 drawings completed by patients, staff and community members.

The community open house will run 9 a.m.-5 p.m. Sept. 14 and 9 a.m.-3 p.m. Sept. 15. It’s free and open to the public, but pre-registration is required. Sign up at www.stanfordhealthcares.com. Free parking is available at the Stock Farm Parking Garage, with shuttle access to the hospital entrance.

Ceremonies
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Noonan, a student in the physician assistant program.

Speakers at both ceremonies acknowledged the students’ competitiveness, but cautioned that they must set that tendency aside if they are to learn and grow during their time at Stanford.

“Now is the time to work together and help each other out,” Zachary Stone, a third-year PA student, said at the physician assistant ceremony.

Kimberly DeBruler, a third-year medical student, warned the new MD students that they would fail along the way. She also encouraged them to reach out to students who appear to be struggling. “Check on each other. Text that person who didn’t make it to the party, or who stopped coming to class,” she said.

Compassion and science

Faculty speakers reminded the students that caring for patients calls for compassion as well as scientific knowledge. Abraham Verghese, MD, professor of medicine and a bestselling author, told the physician assistant students that he learned the difference between healing and curing from his own physician assistant when he was practicing in El Paso, Texas. When the physician assistant took him to the home of a young man dying of AIDS, he asked, “What are we doing here?” She responded, “We’re here to do anything. We’re just here to be with the patient.”

He realized that their visit signaled to the patient that his caregivers would not abandon him. In the days before there was an effective treatment for AIDS, he said, “We could heal when we could not cure.”

Arturo Molina, MD, president of the Stanford Medicine Alumni Association, described the relationship between physician and patient as “sacred.” He told the medical students that they would need to practice empathy.

“You will see patients who have had their dreams shattered by illness,” he said. “They will remind you not to take anything for granted.”

At the receptions after the ceremonies, as the new students started feeling more comfortable in their new garb, they said they were looking forward to the years ahead.

“I’m eager to get back to being with patients,” said physician assistant student Alex Topmillet, who worked at a dermatology clinic before arriving at Stanford. “I can’t wait for the clinics.”
By Krista Conger

Irving Weissman, MD, director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine, will receive the 2019 Albany Medical Center Prize in Medicine and Biomedical Research for his pioneering work in stem cell and cancer research, including the identification of blood-forming stem cells and their role in blood cancers, as well as the discovery of a “don’t eat me” signal on the surface of cancer cells that protects them from being eliminated by the immune system.

Weissman is a professor of pathology and of developmental biology at the Stanford School of Medicine and is the director of the Ludwig Center for Cancer Stem Cell Research at Stanford. He will share the $500,000 prize with Bert Vogelstein, MD, who is the Clayton Professor of Oncology and Pathology at Johns Hopkins University’s Sidney Kimmel Cancer Center and the director of the Lustgarten Foundation Pancreatic Cancer Research Laboratory at Johns Hopkins.

Vogelstein is known for discovering that a protein called p53 functions as a tumor suppressor and that its inactivation is critical to the development of many human cancers. He was also the first to demonstrate in colorectal cancer that disease progression is a multistep process resulting from the sequential accumulation of mutations in specific cancer-associated genes.

Together, Weissman and Vogelstein transformed the understanding of cancer biology, cancer progression and disease initiation and progression, paving the way for earlier diagnosis and more effective treatments for a wide range of diseases including leukemia, non-Hodgkin lymphoma and severe combined immunodeficiency (also known as “bubble boy” disease).

The two will be presented with the prize at a Sept. 25 ceremony in Albany, New York.

“Dr. Weissman’s groundbreaking work in advancing our understanding of blood-forming stem cells and cancer has transformed many aspects of modern medicine,” said Lloyd Minor, MD, dean of the Stanford School of Medicine. “The discovery of the ‘don’t eat me’ signal on cancer cells promises to lead to novel clinical applications that will improve human health. We congratulate Dr. Weissman on this well-deserved recognition.”

Adult stem cells are unique in that they can both self-renew and make progenitor cells that give rise to all the specific cell types in a particular tissue of the body. In 1988, Weissman was the first to identify and isolate in mice the hematopoietic, or blood-forming, stem cells that form all the cells of the blood and immune system. In 1992, he and his group found the human blood-forming cells. He and his group have since painstakingly traced the cellular steps leading from a stem cell to each of the many types of mature blood and immune cells in humans, and identified those that go awry in many blood diseases and cancers.

Weissman also identified a molecule called CD47 that exists on the surface of nearly every human cancer cell and protects them from attack by immune cells called macrophages. An antibody targeting CD47, which the researchers have termed a “don’t eat me” signal, is in clinical trials in people with several types of blood and solid cancers. Overexpression of CD47 is also implicated in fibrotic diseases such as scleroderma and surgical adhesions. Recently, Weissman identified additional “don’t eat me” signals, each of which is expressed by particular types of cancers.

“I am especially honored to share this award with Bert Vogelstein, whose work I have followed for many years and greatly admire,” said Weissman, who is the Virginia and D. K. Ludwig Professor for Clinical Investigation in Cancer Research. “Inspired by his earlier work on colon cancer, we were able to show that nearly all stepwise mutations that lead to the development of leukemia and blood diseases, such as myelodysplastic syndrome, occur in blood-forming stem cells, apparently hitchiking in these self-renewing cells to form disease clones. It’s a fantastic feeling to join the group of highly accomplished past recipients of the Albany Prize.”

The Albany Prize is funded by a $500 million gift from New York City philanthropist Morris Silverman. It has been awarded since 2001 to encourage and recognize extraordinary and sustained contributions to improving health care and promoting biomedical research with translational benefits for better patient care. In 2015, Karl Deisseroth, MD, PhD, Stanford professor of bioengineering and of psychiatry and behavioral sciences, received the award.
Hypertension continued from page 1

Pulmonary hypertension occurs when the arteries that transport blood from the heart to the lungs mysteriously thicken and become increasingly clogged, thereby weakening the heart, which has to pump extra hard to get blood to flow through the body. After diagnosis, most patients face a prognosis of just a few years of life before they die of heart failure. Some patients are born with the disease, but often it strikes in later life.

Treatment is limited to vasodilators, drugs that cause the smooth muscle cells of the diseased blood vessels in the lungs to relax, permitting more blood to flow through. These drugs help to extend survival and reduce very serious symptoms, but they are not a cure. Thus, scientists have been searching for other treatments.

Past research has shown that the majority of patients with the inherited form of pulmonary hyper- tension carry a mutation in the gene BMPR2. Whether the mutation plays a role in causing the disease has been unclear. Surprisingly, 80% of people with the mutation don’t get the disease and remain perfectly healthy. Nicolls said.

A hypothesis

Based on previous research into inflammation in the lungs, the Stanford researchers hypothesized that an inflammation-producing pathway may provide the second “hit” that triggers the mutation to cause the disease in certain patients. To test the theory, the researchers developed a rat model with a mutation in the BMPR2 gene. They followed the rats for a year, and found that the animals remained healthy. Yet when the rats were injected with a virus carrying the 5LO enzyme that triggered temporary lung inflammation, they developed pulmonary hypertension.

“At first, the rats with this mutation should have survived, as they were healthy, running around the cage,” Tien said. “Then we administered the virus into their lungs, which stimulated the production of inflammation in the vessels of the lung, and they got really sick.”

The lung inflammation caused by the virus usually lasts only a few days. But when the rats are treated with 5LO and, in humans, can also be caused by environmental triggers, such as a severe flu or bacterial infection or even hiking to high altitudes. However, in the genetically susceptible rats, the virus led to permanent inflammation, damaging the lung vessels and causing a lethal form of pulmonary hypertension.

“Anemia, a bad flu, temporary types of lung inflammation, smoking and pancreatitis — all can be 5-LO mediated,” Tien said. “This type of inflammation normally has a pretty short life span. But in these rats, even after the injected virus caused the damage to the endothelial cells in the lining of the blood vessels continued to proliferate the cells, becoming the bad player, and they continued to proliferate the inflammation.”

These results indicate that limiting potential environmental causes of lung inflammation in patients with a genetic risk for pulmonary hypertension may help prevent the development of the disease, the study said.

Other Stanford co-authors of the study are Xingao Jiang, MD, PhD, project leader; Yon Sung, MD, clinical assistant professor of pulmonary and critical care medicine; Lusia Liu, MD, PhD; Shravani Pasupneti, MD, instructor of medicine; research assistants Petra Dahms, Allen Liu, Eric Shuff and Yel Kuo; and chemist Chang-Chun Hsia, PhD, director of laboratory operations; Roham Zamanian, MD, associate professor of medicine; Michael Snyder, MD, professor and chair of genetics; and Marlene Rabinovitch, MD, professor of pediatric cardiology.

Researchers at the University of Michigan, Virginia Commonwealth University, the University Paris-Sud and the University Paris-Saclay also contributed to the study. This work was funded by the National Institutes of Health and the Vera Moiseyof Wall Center.

Nicolls and Tian are co-investors on a patent titled “Treatment of Pulmonary Hypertension using Anxiolytic Inhibitors.”

Nicolls is a member of the Stanford Cancer Institute.

The Stanford Department of Medicine also supported the work.
Bacteria

continued from page 1

L. Horton Professorship, is the senior author. Lead authorship is shared by postdoctoral scholars Thomas E. Noack, PhD, and Marie Cortese, PhD, and Nadine Rouphael, MD, PhD, associate professor of medicine and infectious disease at Emory University.

Inspired by a mouse study

The idea that the trillions of bacteria inhabiting the human gut play a role in our health is far from new, but it is only recently that the powerful data in human beings has been sparse, with causal evidence coming mainly from studies in mice.

The new study was inspired by a mouse study that Pulendran and his colleagues conducted in 2011. Those investigators found that mice raised in a germ-free environment had impaired antibody responses to influenza vaccination. The higher the counts of gut bacteria, the better the mouse did.

But this time, they selected only individuals whose low levels of antibody responses indicated low prior exposure to the virus or to the vaccine itself. None of the new recruits had gotten flu vaccinations for at least the past three years. Five individuals were given broad-spectrum antibiotics, as in the previous year. The other six served as controls.

But this time, they selected only individuals whose low levels of antibodies indicated low prior exposure to the virus or to the vaccine itself. None of the new recruits had gotten flu vaccinations for at least the past three years. Five individuals were given broad-spectrum antibiotics, as in the previous year. The other six served as controls. All 11 got vaccinated.

After a two-week incubation period, samples from all participants were collected. Bacteria in the feces were cultured and identified, and a metabolomic analysis of the stools was performed.

The researchers found that the individuals who received antibiotics had lost not only the antibody responses but also the metabolites that supported those responses. In contrast, the individuals who did not receive antibiotics maintained their antibody responses and metabolites.

The results suggest that the metabolites produced by the gut microbiome play a crucial role in maintaining antibody responses to influenza vaccination. The findings also suggest that antibiotic use may disrupt the gut microbiome, leading to reduced antibody responses.

This study is ongoing, and the researchers hope to extend it to a larger group of participants to confirm these findings.
Christopher Almond, MD, was promoted to professor of pediatrics, effective May 1. He directs clinical research in the Pediatric Advanced Care Therapies Program at Lucile Packard Children’s Hospital Stanford. His primary research interests are in multicenter clinical trials and learning health networks in pediatric heart failure, ventricular assist device support and cardiac transplantation.

Manuel Amieva, MD, PhD, was promoted to professor of pediatrics and of microbiology and immunology, effective July 1. He specializes in treating pediatric infectious diseases. His research focuses on understanding how bacteria colonize our skin and gastrointestinal epithelium, and how that can lead to infection and disease.

Leah Backhus, MD, associate professor of cardiothoracic surgery, received the Dr. Dwight C. McGoon Award from the Thoracic Surgery Residents Association for her commitment to teaching and mentoring. She also received the Levi Watkins Innovation and Leadership Development Scholarship from the Thoracic Surgery Foundation. The Watkins award includes $5,000 to cover travel expenses incurred for the purpose of learning new thoracic surgery techniques.

Alister Boettiger, PhD, assistant professor of developmental biology, and Leslie Mateo, a graduate student in developmental biology, were awarded a William J. and Marylou Benham Fellowship for Advanced Study. They will receive $50,000 a year for up to three years to promote inclusivity in laboratories and increase diversity in the life sciences.

Catherine Curtin, MD, was promoted to professor of plastic and reconstructive surgery, effective July 1. She specializes in peripheral nerve surgery and upper limb reconstruction. Her research focuses on reducing pain and improving function for people with peripheral nerve injury, and improving upper limb function for people with spinal cord injury.

Lisa Giocomo, PhD, assistant professor of neurobiology, received a scholars award from the Valley Foundation. The $300,000 grant is for basic biomedical research. Giocomo researches the neural mechanisms of clotsing disorders. CMP-Neu5Ac is made and how it regulates platelet number and function, with the goal of illuminating fundamental aspects of platelet biology and developing effective therapies for bleeding and clotting disorders.

K.C. Huang, PhD, was promoted to professor of bioengineering and of microbiology and immunology, effective June 1. His research investigates the physical mechanisms of cell growth and the ecological principles underlying microbial community assembly and function.

Elizabeth Kidd, MD, was promoted to associate professor of radiation oncology, effective Aug. 1. Her clinical focus is treating gynecologic cancer and performing brachytherapy. Her research aims to optimize and individualize treatment for gynecologic cancers to improve disease control and quality of life for patients.

Shivaani Kummar, MD, professor of oncology and radiology, was awarded the 2019 David R. Gandara Lectureship on Developmental Therapeutics from the UC-Davis Comprehensive Cancer Center. The award is for visionary leadership in developmental therapeutics for cancer.

Robbie Mazajian, MD, was appointed assistant professor of pediatrics, effective June 1. His research focuses on optimizing chimeric antigen receptor T cell therapies to treat neuroblastoma, sarcomas and brain tumors, particularly for pediatric cancer patients.

Philip Pizzo, MD, the David and Susan Heckerman Professor and professor of microbiology and immunology, received the New York Academy of Medicine’s John Stearns Medal for Distinguished Contributions in Clinical Practice. The award is for extraordinary, career-long contributions to the clinical practice of medicine.

Elsie Ross, MD, assistant professor of surgery, was awarded a K01 grant from the National Institutes of Health. The five-year, $162,000-per-year grant will support her study of artificial intelligence to enable early identification and treatment of peripheral artery disease.

Birgitte Schuele, MD, associate professor of pathology, was awarded a $100,000 grant from the Neureman’s Family Fund. The grant supports her research into neuronal microcircuits in Parkinson’s disease.

Sharon Sha, PhD, associate professor of neurology and neurological sciences, was appointed to the Alzheimer’s Prevention and Preparedness Task Force for the State of California. The task force presents recommendations to the governor on how local communities, private organizations, businesses, government and families can prepare for the rise in the number of cases of Alzheimer’s disease.

Katherine Travis, PhD, was appointed assistant professor (research) of pediatrics, effective July 1. Her research uses advanced neuroimaging techniques to examine how white matter structures of the brain contribute to reading and language skills in children, with the goal of identifying and developing interventions for children who are at greatest risk of learning difficulties.

Christopher Almond
Manual Amieva
Leah Backhus
Alister Boettiger
Leslie Mateo

Catherine Curtin
Lisa Giocomo
Jeremy Heit

K.C. Huang
Elizabeth Kidd

Shivaani Kummar
Robbie Mazajian
Philipp Pizzo
Elsie Ross
Birgitte Schuele
Sharon Sha
Katherine Travis