Algorithm rivals radiologists in screening X-rays for particular diseases, study finds

By Hanae Armitage

A new artificial intelligence algorithm can reliably screen chest X-rays for more than a dozen types of disease, and it does so in less time than it takes to read this sentence, according to a new study led by Stanford researchers.

The algorithm, dubbed CheXNeXt, is the first to simultaneously evaluate X-rays for a multitude of possible maladies and return results that are consistent with the readings of radiologists, the study says.

Scientists trained the algorithm to detect 14 different pathologies: For 10 diseases, the algorithm performed just as well as radiologists; for three, it underperformed compared with radiologists; and for one, the algorithm outdid the experts.

“Usually, we see AI algorithms that can detect a brain hemorrhage or a wrist fracture — a very narrow scope for single-use cases,” said Matthew Lungren, MD, MPH, assistant professor of radiology. “But here we’re talking about 14 different pathologies analyzed simultaneously, and it’s all through one algorithm.”

The goal, Lungren said, is to eventually leverage these algorithms to reliably and quickly scan a wide range of image-based medical exams for signs of disease without the backup of professional radiologists. And while that may sound disconcerting, the technology could eventually serve as high-quality digital “consultations” to resource-deprived regions of the world that wouldn’t otherwise have access to a radiologist’s expertise. Likewise, there’s an important role for AI in fully developed health care systems too, Lungren added. Algorithms like CheXNeXt could one day expedite care, empowering primary care doctors to make informed decisions about X-ray diagnostics faster, without having to wait for a radiologist.

“We’re seeking opportunities to get our algorithm trained and validated in a variety of settings to explore both its strengths and blind spots,” said graduate student Pranav Rajpurkar. “The algorithm has evaluated over a 100,000 X-rays so far, but now we want to know how well it would do if we showed it a million X-rays — and not just from one hospital, but from hospitals around the world.”

A paper detailing the findings of the study was published online Nov. 20 in *PLOS Medicine*. Lungren and Andrew Ng, PhD, adjunct professor of computer science at Stanford, share senior authorship of the study. Rajpurkar and fellow graduate student Jeremy Irvin are the lead authors.

Practice makes perfect

Lungren and Ng’s diagnostic algorithm has been in development for more than a year. It builds on their work on a previous iteration of the technology that could outperform radiologists when diagnosing pneumonia from a chest X-ray. Now, they’ve boosted the abilities of the algorithm to flag 14 ailments, including masses, enlarged lymph nodes, breast masses, and abscesses.

By Krista Conger

A cellular culprit — as well as a possible treatment — for a common, sometimes life-threatening post-surgical complication has been identified, by researchers at the School of Medicine.

The condition arises when abnormal fibrous connections called adhesions form after abdominal surgery, tethering organs together or anchoring them to the abdominal wall. Symptoms can include chronic pain, female infertility, bowel obstruction and, occasionally, death. According to the National Institutes of Health, the annual cost of treating post-surgical adhesions in the United States surpasses $1 billion.

“This is a very common surgical complication, but it’s not been well-studied,” said Jonathan Tsai, MD, PhD, a former medical student at Stanford and now resident physician at Brigham and Women’s Hospital in Boston.

“Until now, it wasn’t even known what cell type was involved in originating the adhesions. Now we’ve come up with a way to isolate the injured tissue before they form the adhesions, and identify the molecular pathways involved.”

The researchers developed and studied a mouse model of adhesion formation to identify the cell responsible for the initial steps. They also showed that an antibody-based therapy could break down those that had already formed. The hope is that similar techniques could help treat post-surgical adhesions in humans.

Tsai is the lead author of the work, which was published Nov. 28 in *Science Translational Medicine*. Yavul Rinkevich, PhD, a former Stanford postdoctoral scholar, and Irving Weissman, MD, professor of pathology and of developmental biology, share senior authorship of the study. Weissman is the director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Common surgical complication can be treated, prevented in mice, scientists say

See ADHESIONS, page 6

See X-RAY, page 7

‘Chemo brain’ caused by malfunction in three types of brain cells

See CHEMO, page 7
Opioid prescriptions from dentists linked to youth addiction risk

By Erin Digitaile

Teenagers and young adults who receive initial opioid prescriptions from their dentists are at increased risk for opioid addiction in the following year, a study from the School of Medicine has found.

The study, which was published Dec. 3 in JAMA Internal Medicine, examined opioid use and abuse in a large group of privately insured patients from across the United States. Of nearly 15,000 young people who received initial opioid prescriptions from their dentists in 2015, 6.8 percent had additional opioids prescribed between 90 and 365 days later, and 5.8 percent were diagnosed with opioid abuse during the 12 months after the initial prescription. In a comparison group that did not receive an opioid prescription from their dentists, 0.1 percent got another opioid prescription and 0.4 percent were diagnosed with opioid abuse over the same period.

The research team explored the risk of opioid prescriptions from their dentists in teenagers and young adults. Many patients are prescribed opioids to manage pain after wisdom tooth removal.

“This work raises two really important related but separate questions: Do we need opioids, and do we need the procedure?” said the study’s lead author, Alan Schroeder, MD, clinical professor of pediatrics at Stanford.

Beneficial procedure?

Though extremely common, wisdom tooth extractions are not well-studied, and the balance of risks and benefits is not clear, Schroeder said. His overall research focus is “safely doing less” — trying to identify common interventions in pediatrics that may have unfavorable risk-benefit profiles and asking if they could be simplified or eliminated for patient safety. Removal of disease-free wisdom teeth has not been studied thoroughly enough to determine whether it benefits patients, according to a 2016 Cochrane review of the subject.

The research team used a database that contains de-identified information on millions of privately insured patients from across the United States. The researchers focused on patients who were 16 to 25 years old in 2015, as these patients are at the highest risk of new opioid prescription and abuse.

As all patients who had received other opioid prescriptions before getting a prescription from a dentist. This left 14,888 young patients who got an initial opioid prescription in 2015 from a dental practitioner. The median number of pills prescribed was 20.

Of nearly 15,000 teenagers and young adults initially prescribed opioids from their dentists in 2015, 5.8 percent were diagnosed with opioid abuse during the following 12 months, a new study found.

Tracking the opioid use

Seventy-five percent of the opioid prescriptions were for hydrocodone-acetaminophen, commonly known by the brand name Lortab, Norco or Vicodin. In the 12 months prior to the real or phantom opioid prescription date, about 3 percent of subjects in each group had diagnosed with substance abuse of nonopioid substances.

Compared with patients in the control group, the group that received dental opioids had significantly greater rates of continuing opioid use and abuse.

“Almost 7 percent of these patients had new, persistent use at least three months after the initial prescription and almost 6 percent had an opioid abuse diagnosis,” Schroeder said. “That's pretty alarming.”

The youngest patients, ages 16 to 18, were significantly more likely to have persistent opioid use than the oldest patients, ages 22 to 25. Female patients were more likely to have persistent opioid use, while patients of Asian race/ethnicity were less likely to have persistent use.

Follow-up research is needed to determine whether opioids are the safest method of treating pain from wisdom tooth extractions, and whether the extractions themselves are always necessary, Schroeder said. “I think we should ask, No. 1, Why are we prescribing such a high quantity of opioids so frequently? And No. 2, Are all the procedures that are driving these opioid prescriptions necessary?” he said.

The study was funded by the Friedenrich Diabetes Fund and the National Institutes of Health.

The research was funded by Stanford’s Department of Pediatrics.

Zinc used to target insulin-producing cells with regenerative drug

By Nathan Collins

An insulin injection can manage diabetes symptoms, but actually curing the disease would mean healing cells in the pancreas that produce insulin, a hormone that regulates the amount of sugar in blood.

One promising approach may be to stimulate the regeneration of those cells with drugs. But there’s a major obstacle: The growth triggers by the drug is willowy, affecting tissues not just in the pancreas but throughout the body.

Now, a team of Stanford endocrinologists and chemists has taken a step toward targeting the right cells more precisely, using a property that researchers have long known about but never exploited for treatment: Beta cells, the insulin-producing cells in the pancreas, have a particularly strong taste for zinc.

In a study published online Dec. 6 in Cell Chemical Biology, Stanford researchers used that fact to selectively deliver a drug to beta cells. Justin Annes, MD, PhD, assistant professor of medicine, is the senior author. Graduate student Timothy Horton is the lead author.

The method hasn’t been optimized yet, and it isn’t anywhere near ready for clinical use. “We’re at the earliest stages,” Annes said. But in a field where the main options are insulin injections and insulin pumps, which continuously deliver the hormone through a catheter, it could pave the way to more appealing alternatives.

Seeding regeneration

Diabetes is a disease in which the body can’t produce enough insulin to maintain normal blood sugar levels. For years, Annes’ goal has been to develop a medication that would promote the regeneration of insulin-producing beta cells. Although some researchers deemed it impossible, Annes and his colleagues recently succeeded in creating specific molecules that make beta cells divide and produce more beta cells.

That advance might have given new hope to diabetes patients, but there was a catch: The way to get beta cells to start dividing and replicating is the same way to get lots of other cells to divide and replicate. In other words, researchers might be able boost the number of beta cells in the pancreas, but in the process they’d get lots of other cell types to replicate as well.

The result would be uncontrolled, untargeted replication that would affect lots of other organs beside the pancreas, most likely for the worse.

Then Annes had a thought: Researchers have known since the 1940s that beta cells collect about 1,000 times more zinc than other cells. Researchers have also used that fact to study and visually identify beta cells in pancreatic tissue samples. But Annes reasoned that if he could somehow get a regenerative drug to seek out zinc, he’d get it to beta cells.

Call in the chemists

“The only problem was, I didn’t know how to generate compounds that could test this hypothesis,” Annes said. So he turned to Horton, a graduate student in chemistry, and Mark Smith, a senior research scientist at Stanford ChEM-H and director of its Medicinal Chemistry Knowledge Center.

Together, they devised a strategy based on chelation, a standard technique in chemistry that’s perhaps best known in medicine as a treatment for lead and mercury poisoning. In such cases, chelation is used to bind a drug that forms tight bonds with the metals, which can then be flushed out of the body.

Annes, Horton and Smith aimed to use a zinc-chelating agent, which would bind to zinc wherever it runs into it, to deliver a drug to zinc-loving cells, but first they needed to know how much zinc-accumulating agent itself would accumulate in beta cells. After initial lab tests showed it did, they attached a beta-cell regenerating drug to the zinc-chelating agent, and found that the drug would also build up in beta cells in a lab dish.

The team also showed that its zinc-chelation approach amased more of the drug in beta cells than other cell types. When the drug was administered to rats, including beta cells, in a dish, the beta cells regenerates about 50 percent more than other cells of the same type.

That’s not to say that a treatment is around the corner, the researchers caution. “This is the first demonstration of a selective delivery of replication drug to beta cells,” Annes said, “and it’s not sufficient for therapeutic applications.” But the team believes the approach could one day lead to treatments if they can improve its beta-cell selectivity.

Annes is a member of Stanford Bio-X, the Stanford Maternal and Child Health Research Institute, the Sansum Cancer Research Institute and Stanford Bio-X.

Other Stanford authors are Smith; postdoctoral scholars Paul Allegritti, PhD, and Sooyeon Lee, PhD; and graduate student Hannah McDole.

The study was funded by the ChEM-H Chemistry/Biology Interface Predoctoral Training Program, Stanford Bio-X, a Stanford interdisciplinary graduate fellowship, the Friedenrich Diabetes Fund and the National Institutes of Health.

Other Stanford researchers also supported the work.

Zinc used to target insulin-producing cells with regenerative drug

Send letters, comments and story ideas to John Sanford at 723-8309 or at johnsanford@stanford.edu. Please also contact him to receive an e-mail version of Inside Stanford Medicine.

December 10, 2018

Inside stanford medicine
Medical school space, finances are focus of town hall meeting

By Julie Greicius

In 20 years, the School of Medicine will need 30 percent more space than it has today. That was the upshot of a Dec. 5 presentation by Niraj Dangoria, associate dean for facilities planning and management, on the opportunities and challenges of managing the school’s growth needs.

Dangoria spoke at a town hall meeting at the Stanford Center for Innovation and Learning and Knowledge that also included a brief update on the school’s financial results for fiscal year 2018.

“At no point do we get so much space that we can say, ‘Oh, our work is done,’” he said. “The space will always be a limited resource.”

Managing space at the school involves balancing faculty growth, workspace needs, the school’s financial health and regulatory constraints, Dangoria said.

Complicated planning

Although the School of Medicine has added about 400,000 square feet of space over the last decade, including the Li Ka Shing Center and the Larry I. Lokey Stem Cell Research Building, its annual faculty growth is exceeding the current available space. Immediate solutions have involved “densifying,” a space, which Dangoria described as “trying to achieve the density functionality and occupation in 15 to 20 percent less space.”

Long-term solutions will require the school to double its off-campus space to accommodate its growing research enterprise, faculty and staff.

On campus, the campus straddles both the Santa Clara County and city of Palo Alto jurisdictions, planning construction is complicated. A 2011 development agreement between Stanford and the construction of the Center for Academic Medicine, set to open in the fall of 2020 on the main campus.

Financial health ‘remains strong’

At the end of the meeting, Lloyd Minor, MD, dean of the School of Medicine, thanked attendants for their service to Stanford Medicine. He then participated in a brief question-and-answer session along with Dangoria, Zelch and Marcia Cohen, MBA, senior associate dean for finance and administration.

By Erin Digitaile

Short home videos can be used to diagnose autism in children, according to a new study from the School of Medicine. The research, which was published online in Pediatrics, expands on a 2014 feasibility study on the topic by the same researchers. In the new study, the scientists employed machine learning to determine which features of children’s behavior should be rated to evaluate autism, using computers to whittle down a long list of behavioral features to those most relevant to the diagnosis. They also devised an algorithm that weights each feature to provide an overall diagnostic score for each child.

“Across the United States, the average waiting list to get access to standard-of-care can last up to a year,” said the study’s senior author, Dennis Hall, PhD, associate professor of pediatrics and bio-medical data science at Stanford. “Using home videos for diagnosis has the potential to streamline the process and make it far more efficient.”

Home videos offer another potential advantage for diagnosing behavioral and developmental disorders, such as autism. “Home video captures the child in his or her natural environment,” Wall said. “The clinical environment can be stark and artificial, and can elicit atypical behaviors from kids.”

Value of early diagnosis

Autism is a developmental disorder characterized by restricted interests and a lack of social relationships, forming social connections. Previous research showed that behavioral therapies for autism work best when started before age 5, but long waits for testing make it difficult for families to access timely treatment. Current diagnostics are time-intensive, requiring one-on-one assessment with an autism specialist. Clinicians spend a few hours per patient assessing dozens of aspects of the child’s behavior.

In the new study, the researchers devised and tested eight machine-learning models for diagnosing autism from short videos. Each model consisted of a set of algorithms that included five to 12 features of children’s behavior and scored each child with an overall numerical scoring index indicating whether the child had autism.

Whereas in the prior study, the researchers asked families recruited through social media and autism listservs to submit a video of their child with autism (average age 4 years, 10 months) and 46 videos of children without autism.

One model, a logistic regression model, performed best, identifying autism with 94.5 percent accuracy. The researchers repeated the experiment with 60 children with autism and 33 children without autism.

The researchers are now repeating their investigation with home videos of young children in Bangladesh to see how well their mathematical models translate across cultures.

Home videos of children can be scored to diagnose autism

All of the yes/no questions were based on behavioral characteristics used in standard autism screening tools.

Nine raters scored 50 of the videos, and the researchers used these results to determine that three raters were the minimum number needed to generate a reliable score. The remaining videos were randomly assigned to the raters, with three raters scoring each video.

On average, watching and scoring the videos took the raters 4 minutes each. The data for each video, consisting of the 30 yes/no answers to questions about the child’s behavior, was fed into the eight mathematical models.

One model, a logistic regression model that used five behavioral characteristics, performed best, identifying autism with 88.9 percent accuracy, including correctly labeling 94.5 percent of children with autism and 77.4 percent of children without autism.

To validate their findings, the researchers repeated the experiment with an additional 66 videos — 35 featuring children with autism and 31 with children who did not have autism. The same model performed best, with correct identification of 87.8 percent of children with autism and 72.7 percent of children without autism.

“We showed that we can identify a small set of behavioral features that have high alignment with the clinical outcome,” the researchers noted. “Our model independently score these features in a virtual environment online in minutes, and that the model we used to combine those features is effective in producing a score that matches the clinical outcome,” Wall said. The final scores are not just a “yes or no” autism diagnosis, he added; instead, the numerical scores may hold information about the severity of the disorder and be of value for tracking progress over time.

Providing tool for pediatricians

Woll hopes simple scoring systems for home videos will help streamline the process of autism diagnosis. “This could be used in general pediatric settings, or in well-baby checkups,” he said, adding that video scores could be plotted over time and compared with the general population, similar to how a child’s height and weight are plotted on a growth chart.

The 60-minute tool is a dream that is a tool like this will give general pediatricians more confidence in making diagnostic decisions and help them achieve developmental disorders,” he said. For a very young child — at an age when autism can be difficult to distinguish from normal development — the doctor’s decision might be to engage in watchful waiting, but with the advantage of having more developmentally targeted screening, and difficulty for later evaluations. In other cases, it might be clear that a child needs to immediately begin autism treatment, or needs to be referred to a specialist for a more detailed diagnostic evaluation.

The researchers are now repeating their investigation with home videos of young children in Bangladesh to see how well their mathematical models translate across cultures.
By Krista Conger

A mammalian protein similar in structure to the active component of honeybee royal jelly could help keep stem cells youthful, a finding that could have implications for future therapies. The researchers showed that there are close parallels between the human and Botryllus blood systems, offering an excellent model for studying many biological phenomena in mammals.

Kevin Wang holds a flask of cells that have been engineered to produce the Regina protein, a mammalian protein similar in structure to the active component of honeybee royal jelly.

Honeybee protein keeps stem cells youthful, study finds

Sea invertebrate sheds light on evolution of immune system

By Christopher Vaughan

Botryllus schlosseri, a marine invertebrate that lives in underwater colonies resembling clusters of tiny petals clinging to rocks, has a blood-forming system with uncanny similarities to that of humans, according to scientists at Stanford University.

In a study published online Dec. 5 in Nature, the researchers report that these lowly sea creatures are scientific “treasure boxes” that may provide a way to understand our own blood-forming system, improve our immune function and find new immune-associated tools for biological discovery.

The mammalian and Botryllus blood-forming systems also share hundreds of homologous genes, even though the two species are separated by over 500 million years of evolution, said former postdoctoral scholar Benyamin Rosental, PhD.

Rosental shares leadership of the study with graduate student Mark Kowarsky. The senior authors are Irving Weissman, MD, the Virginia and D.K. Ludwig Professor for Clinical Innovation in Cancer Research and professor of pathology and of developmental biology; Stephen Quake, PhD, the Lee Otisson Professor in the School of Engineering and professor of bioengineering and of applied physics; and senior research scientist Ayret Voskoboinik, PhD.

The researchers isolated the Botryllus stem cells that are the foundation of its blood and immune system, as well as the progenitor cells they make on their way to becoming adult blood and immune cells. “Out of all the invertebrates, the Botryllus blood stem cells and progenitors are the most similar to vertebrate blood cells, so it is possible, if not likely, that they are the ‘missing link’ between vertebrates and invertebrates,” said Weissman, who also directs the Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Ludwig Cancer Center at Stanford.

Botryllus is an organism with many odd characteristics. It lives part of its life as a free-swimming chordate and part of its life as a sessile organism on the subtidal surface. Under the microscope, a Botryllus colony looks like a bouquet of flowers, although in reality each “petal” is a separate organism with its own heart, gills, digestive system and hormonal activity, it prevents the activation of a rejection process that is similar to the way that the human immune system’s natural killer cells attacks tissues that are not “self.”

The discovery of such strong parallels between the two systems offers researchers an excellent model for studying many biological phenomena in mammals, the researchers said. “To their surprise, Wang and colleagues found that royalactin blocked differentiation even in the absence of immunity.”

For answers, the researchers turned to a database that infers the three-dimensional structure of proteins. Like a lock and key, many proteins work by fitting precisely together with other proteins or molecules. The scientists wondered whether there might be another protein in mammals that mimics the shape, but not the function of royalactin.

See JELLY, page 8

DECEMBER 10, 2018            INSIDE STANFORD MEDICINE

4
Stanford Medicine staff helps humans, animals in wake of Camp Fire

By Susan Coppa and Susan Ipaktchian

Andre Burnier, MD, hadn’t taken his boots off in 24 hours. Even when he grabbed a nap on a cot under a Red Cross blanket, he kept his boots on so he could be ready at a moment’s notice to attend to patients.

It was Nov. 28. Earlier that day, Burnier, a second-year resident in the Department of Emergency Medicine at Stanford, had treated an elderly man whose home had been destroyed in the Camp Fire, the deadliest wildfire in California history. “I’m sure he was ex-pectant to pass away on the path to the hospital,” Burnier said. “Everyone has a story, and the vast majority of their prob-lèmes are the fire.”

Burnier had deployed with the Stanford Emergency Medicine Program for Emergency Response (SEMPER), to provide medical support for people displaced by the fire, which started Nov. 8 in Butte County, California, and was not fully contained until Nov. 25. Since be-coming established in 2010, SEMPER has deployed teams of Stanford physicians and nurses to areas hit by disasters, such as earthquakes and hurricanes, around the world.

In addition to members of SEMPER, other Stanford Medicine employees have helped out in the wake of the fire’s destruction, including a clinical assistant professor of emergency medicine who serves as the physician for Task Force 3 of the Federal Emergency Management Agency and veterinary technicians with the medical school’s Department of Comparative Medicine.

‘Second wave’ of medical support

The fire was responsible for at least 85 deaths. It destroyed nearly 14,000 homes and scorched 153,000 acres of land. More than 50,000 people were displaced. Some are still in shelters with nowhere else to go. The California Emergency Medical Services Authority called in SEMPER to provide a “second wave” of medical sup-port for displaced residents.

“We are not treating high trauma,” said Ian Brown, MD, clinical associate professor of emergency medicine at Stanford and a leader of the SEMPER team that was volunteering Nov. 25-28. “Our biggest concern is in-fectious disease and chronic conditions, like diabetes, that have come untreated.”

Carol Conceicao, MD, a second-year emergency medicine resident at Stanford, treated a pregnant patient at the shelter, but also set up a prenatal care plan for her. “We are setting these patients up for life after this disaster,” Conceicao said.

Members of the SEMPER team stationed at shelters on the Glenn County and Butte County fairgrounds, Joselinda Landon, one of two nurses on the team, acknowledged that the work was demanding. “Someone needs to sleep. There are just no time slots,” she said. “We might be up for 24 hours; we don’t care.”

She said her focus was on the fire victims and what they were facing. “The holidays are coming,” she said, nodding to people gathered at the shelter. “They don’t have a home. Their family is gone. I can feel their pain.”

‘No way to outrun it’

The Camp Fire was also different than anything Justin Lemieux, MD, had experienced. A Stanford emer-gency medicine physician and veteran of several relief missions, he said he had never witnessed anything like the Camp Fire, the deadliest wildfire in California history. “I’m sure he was ex-pectant to pass away on the path to the hospital,” Burnier said. “Everyone has a story, and the vast majority of their prob-lèmes are the fire.”

Lemieux was part of the first wave of responders. He deployed as the team doctor for FEMA Task Force 3 about a week following the outbreak of the Camp Fire. (Above) Andre Burnier, Nancy Glieber and Joselinda Landon volunteered in November with the Stanford Emergency Medicine Program for Emergency Response to provide medical support for Butte County residents displaced by the fire.

Lemieux, walked slowly and methodically through ruined neighborhoods, searching from one end to the other for survivors or remains, over collapsed structures, caved roofs and sharp debris. Other hazards included downed power lines and burned, overhanging tree branches. The soil had weakened in spots, and search-ers moved cautiously to avoid falling in unseen septic tanks. The fire was still raging in areas, and the smoke was bad. But even worse, many buildings had asbestos and chemical products that had burned, potentially ex-posing team members to toxins. Lemieux and his team members wore hood-to-toe protective equipment, in-cluding face masks.

Sadly, the real service we were doing is searching, not rescuing,” Lemieux said.

Lemieux treated mostly foot injuries caused by the dangerous terrain. One of the first injuries came the night of Nov. 18 — to George, a highly-trained Ma-rine’s search dog. “These dogs are incredibly stoic,” Lemieux said. “No way to outrun it.”

Lemieux had deployed with the Stanford Emergency Medicine Program for Emergency Response to provide medical support for Butte County residents displaced by the fire.

Back at the base of operations, two team members held George, more to reassure him than to restrain him, as Lemieux stitched his leg. “When I finished, George jumped up and licked the hell out of my face,” Lemieux said. “He seemed to know my job was to help him.”

Lemieux and the team were onsite in Magalia for more than a week, spending Thanksgiving in tents away from family and friends.

Caring for injured animals

After seeing the reports of animals injured in last year’s fires in Northern California’s wine country, Ofera Satterfield and Candice Alfaro knew they wanted to be able to help in a future disaster.

The two veterinary technicians in the Department of Comparative Medicine at Stanford were planning to graduate earlier this year and became part of a volunteer corps that could help during emergency situations. When the call for assistance was made following the Camp Fire, each of the women spent a daylong shift caring for the cats, dogs, birds and other small animals that were brought to a hangar at the Chico airport.

During Alfaro’s shift on Nov. 19, she helped triage the animals as they were brought in, and then spent hours caring for cats that had been burned. She said many of the cats were extremely de-hydrated after being on their own for days without food or water.

Satterfield helped care for a variety of animals during her Nov. 24 shift, including a chinchilla that needed a dust bath, which helps remove dirt and excess skin oil from the rodent’s fur.

Although the animals were injured and could not return to their homes, Satterfield and Alfaro said the dogs and cats they treated seemed to realize that the volunteers were there to help them. “They were pretty mellow,” Satterfield said.

Both of the women said it was difficult to watch dis-traught Butte County resi-dents come to the makeshift shelter in the hope of finding their lost pets. “People had lost their homes, and they were still searching for their pets,” Satterfield said. “It was hard to see them go in and then leave without finding their pets.”

Both Alfaro and Satterfield said the fire reinforced why microchipping and registering pets is important. “Some people might not think they need to microchip their pet if they keep the pet inside most of the time,” Satterfield said, but in the case of a fire, animals can quickly scatter. The volunteers worked with animal control officials to document each of the wounded ani-mals to help owners locate their pets.

The Department of Comparative Medicine donated supplies for the animals; Michael Remzi, director of fi-nance and administration for the department, delivered the supplies to Chico, in Butte County.

Volunteers from the North Valley Animal Disaster Group and the California Veterinary Medical Reserve Corps have provided for animals affected by the fires. Information about donating to the organizations is available online at https://www.navd.org and https://california-vertebratemedical-reserve-corps-cvmc/california-vertebratemedical-reserve-corps-cvmc-information/.

Botryllus continued from page 4

the cells in individual organisms interact when one organism mounts an immune attack against the other, or the two individuals fuse blood vessels. This could provide sci-entists with a better understanding of why an organism accepts or rejects foreign cells, knowledge that could give insights into transplant acceptance and rejec-tion, Voskoboinik said.

“With its primitive but effective immune system, Botryllus may also give us insights into how we can boost our own immune responses to pathogens and cancer,” Voskoboinik said. “But in addition to any practical benefits this research may produce, we are de- lighted to explore this important guidance on one of the most basic questions in biology: how does an organism understand the evolution of vertebrates, and of their blood-forming and immune systems. Isn’t that what curiosity-driven science is supposed to do?”

Other Stanford authors are Garry Nolan, PhD, professor of microbiology and immunology; Aaron Newman, PhD, assistant professor of biomedical data science; Rahul Sinha, PhD, instructor at the Institute for Stem Cell Biology and Regenerative Medi-cine; former postdoctoral scholars Daniel Corey, MD, PhD, Norma Neff, PhD, and Jun Seita, PhD; former graduate students Jonathan Tsai, MD, PhD, Nathaniel Clarke, PhD, and Shih-Tu Chen, PhD; research fund-ing and financial support from the National Institute of Biomedical Imaging and Bioengineering, the American Heart Association, and the Human Frontier Science Program Organization.

Stanford’s departments of Pathology, of Developmental Biology, of Bioengineering and of Applied Physics also supported the work.
Progress in peanut-allergy immunotherapy

An interdisciplinary team of School of Medicine researchers has received a four-year, $9.6 million grant to probe the interactions between the brain and blood vessels in order to develop a better understanding of age-related brain diseases like Alzheimer’s disease.

The Stanford team, which includes 13 faculty members, is one of only three groups nationwide to receive such an award from the American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment, a collaborative funding initiative sponsored by the AHA and the Paul G. Allen Initiative, a division of the Allen Institute.

The project will focus on the influence of immune factors and systemic inflammation on the brain, said principal investigator Tony Wyss-Coray, PhD, professor of neurology and neuroscientific studies.

An age-related change is the increase in the Abelson-related signal transducer and activator of transcription (Abt1) in astrocytes, which are brain cells that send out long extensions called processes and form connections with other cells in the brain.

The project’s unique approach to systematically investigate the connections between the brain and blood vessels in order to better understand how age-related diseases like Alzheimer’s disease are caused.

The first experiments involved testing the effects of drugs on animal models of Alzheimer’s disease. The researchers found that drugs that reduce inflammation in the brain, such as non-steroidal anti-inflammatory drugs (NSAIDs), can improve cognitive function and reduce the severity of the disease.

The researchers are now using brain imaging and genetic studies to identify specific abnormalities in the brain that are associated with Alzheimer’s disease.

One potential target is the role of certain immune cells, called microglia, in the development of Alzheimer’s disease. These cells are involved in the inflammation associated with the disease and may have a role in the process of synaptic pruning, which is essential for maintaining healthy brain function.

In the future, the researchers hope to identify new therapeutic targets and develop new treatments for Alzheimer’s disease that can slow or stop the progression of the disease.

Grant for research on vascular risk factors for brain aging, dementia

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The first experiments involved testing the effects of drugs on animal models of Alzheimer’s disease. The researchers found that drugs that reduce inflammation in the brain, such as non-steroidal anti-inflammatory drugs (NSAIDs), can improve cognitive function and reduce the severity of the disease.

The researchers are now using brain imaging and genetic studies to identify specific abnormalities in the brain that are associated with Alzheimer’s disease.

One potential target is the role of certain immune cells, called microglia, in the development of Alzheimer’s disease. These cells are involved in the inflammation associated with the disease and may have a role in the process of synaptic pruning, which is essential for maintaining healthy brain function.

In the future, the researchers hope to identify new therapeutic targets and develop new treatments for Alzheimer’s disease that can slow or stop the progression of the disease.
in the United States, a figure expected to reach 20 million by 2026, according to the National Cancer Institute. But the cognitive side effects of cancer treatment are often debilitating and prolonged: Adults may be unable to return to work, and children often struggle in school. “We know that they’re alive, but their quality of life is really suffering,” said the study’s lead author, Erin Gibson, PhD, a research scientist at Stanford. “If we can do anything to improve quality of life, there is a huge population that could benefit.”

Scientists have long known that drugs like methotrexate impair all of the body’s rapidly dividing cells, but how such drugs affect the function of brain cells has been poorly understood.

“Cognitive dysfunction after cancer therapy is a real and recognized syndrome,” said Michelle Monje, MD, PhD, associate professor of neurology and neurological sciences and the study’s senior author. “In addition to existing symptomatic therapies—which many patients don’t know about—we are now homing in on potential interventions to promote normalization of the disorders induced by cancer drugs. There’s real hope that we can intervene, induce regeneration and prevent damage in the brain.”

Chemo brain is especially severe in childhood cancer patients, Monje added, and children have the most to gain from better remedies.

Inside the white matter

In addition to neurons, which transmit nerve impulses, the brain’s white matter contains other cells that help the neurons function. The research focused on three types of those cells: oligodendrocytes, which produce and maintain myelin, the fatty insulating sheath around nerve fibers; astrocytes, which link neurons to their blood supply; and microglia, immune cells that can engulf and destroy foreign invaders in the brain, as well as sculpt neural circuitry. Growing the postmortem frontal lobe brain tissue from children who had and had not received chemotherapy, the researchers showed that there were far fewer oligodendrocyte lineage cells in the brains of the chemotherapy-treated children.

To figure out what was happening to these cells, the researchers injected young mice with methotrexate at levels designed to replicate human exposures during cancer treatment. The mice received three doses at weekly intervals. Four weeks later, the researchers compared the mice’s brains to those of mice that had not received the drug.

Methotrexate chemotheraphy was found to damage the brain’s populations of oligodendrocyte precursor cells. Normally, these cells can migrate and replace any that are lost, but after methotrexate was administered, this self-renewal process did not happen correctly. More than half of the mice’s brains, starting down the path of maturation to oligodendrocytes, but they were getting stuck at the progenitor cell stage. The same problem was seen in mice brains six months after methotrexate was administered.

Transmission electron microscopy of the mouse brains after methotrexate administration revealed deficiencies in the thickness of the myelin insulation around nerve fibers, similar to changes in the brains of humans who have received chemotherapy. Mice exposed to methotrexate also exhibited behavioral problems after four weeks that were similar to humans with chemo brain, including learning impairments (slower performance of their forepaws), signs of anxiety on an “open field” test used to assess how threatened the animal is in an unfamiliar environment, and impaired attention and short-term memory, evidenced by the inability to discern between white and familiar objects—a symptom that persisted for six months after methotrexate was given.

The researchers injected oligodendrocyte precursor cells from healthy animals into the brains of animals that had received methotrexate to see if the cells’ maturation problems were caused by some aspect of the brain environment after chemotherapy. The precursor cells still began maturing at higher-than-normal rates but did not get stuck pathway through the maturation process, indicating that the brain environment was partly responsible for the cells’ abnormal maturation.

Microglial activation

Further study showed that microglia, the tiny immune cells, were persistently activated after methotrexate exposure for at least six months. The activated microglia caused production, immediate inflammation, of the cells that help neurons get nutrients and function properly. Administering a specific antagonist selective for the receptor 2 on microglia to mice that had been treated with methotrexate reversed many of the cognitive symptoms of metho brain and reversed the abnormalities in maturation of oligodendrocyte precursor cells, activation of astrocytes and myelin thickness.

“The biology of this disease really underscores how important intercellular cross talk is,” Monje said. “Every major neural cell type is affected in this pathophysiology. It’s one of the more complex dysfunctions may also underlie other cognitive disorders. “I think that is probably the rule rather than the exception,” she said.

More research is needed to understand exactly how the different cell types interact with each other, when and how medications could be best deployed against chemo brain. “Knowing the cellular and molecular mechanisms that contribute to cognitive dysfunction after cancer therapy, which will help us develop strategies for effective treatment,” Monje said.

“It’s an exciting moment.”

The study’s other Stanford co-authors are MD-PhD student Surya Nagaraja; undergraduate students Alfonso Ocampo, Lydia Tam, Andrea Goldstein, Praveen Pallega and Jacob Greene; former medical student Lauren Wood, MD; postdoctoral scholar Anna Geraghty, PhD; research associates Lijuan Ni and Pamelyn Woo; the late Ben Barnes, MD, PhD, professor of neurology, of development biology and neurological sciences; former postdoc scholar Shane Liddelow, PhD; and Hannes Vogel, MD, professor of pathology and of pediatrics.

Monje is a member of Stanford Bio-X, the Stanford Maternal & Child Health Research Institute, the Stanford Institute for Stem Cell Biology and Regenerative Medicine, and the Wu Tsai Neurosciences Institute. Monje and Vogel are both members of the Stanford Cancer Institute.
Mark Cullen appointed senior associate vice provost for research

By Nathan Collins

Mark Cullen, MD, senior associate dean of research in the School of Medicine, has been named senior associate vice provost for research at Stanford. In the new role, Cullen will advise Kathryn Moler, PhD, vice provost and dean of research, on universitywide research policy and compliance issues, as well as develop strategy on the future of the institutes, independent labs and centers overseen by Moler’s office.

“Mark is a great university citizen. His experience in the school of medicine and expertise in social science research will be invaluable as we think about the future of shared resources and interdisciplinary collaboration at Stanford,” Moler said.

Much of Cullen’s job will be to advise Moler on policy and compliance across the research enterprise, which has changed significantly in nature and scope over the last decade. Among the issues Cullen will focus on, Moler said, is the development and implementation of rules meant to head off the possibility of undue foreign influence on federally funded research while maintaining a spirit of openness and the free exchange of scientific ideas.

Cullen will also spearhead an effort to take stock of the dean of research’s institutes, independent labs and centers, which have expanded both in number and scope. Today, there are 18 such units, covering everything from biosciences to economic policy.

“They’re hugely important for the research enterprise,” Cullen said, adding that with the university’s long-range planning process underway, it is a good time to think strategically about the role they will play in the next decade and beyond.

“Stanford is an unparalleled research environment, and the question is can we move it the next mile. That’s where the heavy lifting is going to come,” said Cullen, professor of medicine, of biomedical data science and of health research and policy. “It’s an opportunity that I think anyone in my position would jump at.”

Cullen came to Stanford in 2009 from Yale University and immediately took on leadership positions. From 2009 to 2015, he served as chief of the division of general medicine disciplines in the School of Medicine. Since 2015, he has directed the Stanford Center for Population Health Sciences and will continue in both that role and as senior of associate dean of research in the School of Medicine. Cullen began his position as senior associate vice provost for research in October.

Ronald Dalman named associate dean for market development

Ronald Dalman, MD, the Widler Clifford Chidester and Elia Rooney Chidester Professor of Surgery and chief of vascular surgery, has been appointed associate dean for market development at the School of Medicine.

In this new role, Dalman will serve as faculty partner for Stanford Health Care market and business development leadership. He will also work closely with clinical chairs, chiefs and staff to identify and optimize network and affiliation agreements across the region to achieve established goals of the integrated strategic plan.

Dalman joined the medical school faculty in 1992. Prior to assuming leadership of the Division of Vascular Surgery in 2005, he served as vascular section chief at the Veterans Affairs Palo Alto Health Care System. In addition to his clinical roles, Dalman serves on the steering committee of the Cardiovascular Research Institute. Dalman directs research lab studies the pathophysiology of abdominal aortic aneurysm disease and is actively engaged in identifying and validating new treatment measures for AAA. He has served for 19 years on the advisory councils of the National Institutes of Health funding as principal investigator or co-principal investigator on AAA-related clinical and translational research studies.

Dalman is the current president of the Society for Vascular Surgery, the world’s largest and oldest professional organization dedicated exclusively to improving vascular health. He will become president-elect of the society in 2019.

Raffi Avedian, MD, was promoted to associate professor of orthopaedic surgery, effective Oct. 1. He specializes in surgery for bone and soft tissue tumors of the musculoskeletal system in children and adults, including limb and joint reconstruction. His research focuses on magnetic-resonance-guided cancer interventions and improving limb salvage techniques. He is also the residency program director for the department.

Maryann Campion, EdD, MS, clinical associate professor of genetics, was elected to a three-year term on the board of directors of the National Society of Genetic Counselors. Beginning in January 2019, she will spend a year each as president-elect, president and immediate past president. The society advances the various roles of genetic counselors in health care by fostering education, research and public policy to ensure the availability of quality genetic services.

Ava Carter, a graduate student in stem cell and regenerative medicine; Theodore Ho, PhD, MS, a postdoctoral scholar in bioengineering; and Hasini Jayatilaka, PhD, a postdoctoral scholar in pediatric hematology-oncology, were included in the 2019 Forbes 30 Under 30 in Science. Kyle Loh, PhD, assistant professor of developmental biology, was included on the 2019 Forbes 30 Under 30 in Healthcare. The Forbes lists feature 600 trailblazers in 20 industries.

Sarah Donaldson, MD, the Catharine and Howard Avery Professor in the School of Medicine and professor of radiation oncology, received the 2018 Radiological Society of North America Gold Medal, the society’s highest honor. She was recognized for contributions to pediatric radiation oncology and for continual mentoring of students, trainees and faculty.

Neville Golden, MD, the Marron and Mary Elizabeth Kendrick Professor in Pediatrics, received the Adele Dellenbaugh Hoffman Award from the American Academy of Pediatrics. The award recognizes achievement in adolescent medicine, and was given to honor his clinical work, research and advocacy for adolescents from diverse backgrounds.

Jennifer Han, MD, was appointed assistant professor of anesthesiology, perioperative and pain medicine, effective Oct. 1. She specializes in treating chronic pelvic pain conditions, and her research interests include developing behavioral and technological interventions to prevent persistent pain and opioid use after surgery.

Boris Heifets, MD, PhD, was appointed assistant professor of anesthesiology, perioperative and pain medicine, effective Oct. 1. He specializes in providing anesthesia for neurological surgery, and his research examines the neural circuits and synaptic mechanisms of new, rapid-acting psychiatric therapies.

Alex Macario, MBA, professor of anesthesiology, perioperative and pain medicine, received the 2018 Excellence in Education Award from the American Society of Anesthesiologists. The award recognizes outstanding contributions to resident and graduate education in anesthesiology.

Anca Pasca, MD, was appointed assistant professor of pediatrics, effective Oct. 1. Her research focuses on understanding molecular mechanisms underlying neurodevelopmental disorders associated with premature birth and neonatal brain injury, with the goal of translating the findings into therapeutics.

Sergiu Pasca, MD, PhD, assistant professor of psychiatry and behavioral sciences, was named a Ben Barres Investigator by the Chan Zuckerberg Initiative. This early career acceleration award, named for the late Stanford neuroscientist, supports early career academic investigators, especially those who are new to neurodegeneration. The five-year, $2.5 million award will support Pasca’s work in developing 3-D organoid systems from human induced pluripotent stem cells with the aim of developing new strategies and tools for modeling brain maturation and neurodegeneration with patient-derived cells.

Kevin Wang, MD, PhD, assistant professor of dermatology, received a 2018 New York Stem Cell Foundation-Robertson Stem Cell Investigator Award. The five-year, $1.5 million award will support his work to understand how dynamic epigenetic changes in chromatin structure impact gene expression during stem cell pluripotency, cellular differentiation and reprogramming. He also was awarded a 2018 Glenn Foundation for Medical Research and American Federation for Aging Research Grant for Junior Faculty. Wang plans to use the $100,000 grant to investigate whether rearranging the spatial interactions of chromosomes can help reverse aging.

 Syracuse University

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Inside Stanford Medicine