INSIDE STANFORD MEDICINE

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A "nutrition surveillance" app could help boost nutrition for children in some of the world's poorest and most remote regions.

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What I did at neuroscience camp this summer

By Ruth Schechter

The teenagers pushed aside their backpacks, adjusted their sweatshirts and looked up at the imposing man in a white coat at the front of the room. He scanned the room and started to pepper his young audience with questions: How many of you wake up tired? How many of you skip sleep to work on homework? How many of you go to sleep after your parents? How many want more sleep?

For each question, every hand in the room shot up.

NORBERT VON DER GROEBEN

Local high school students Alia Rubaie and Gaby Krohn model brains out of Play-Doh during the Clinical Neuroscience Internship Experience.

The class, taught by Rafael Pelayo, MD, a pediatric sleep specialist with the Stanford Center for Sleep Sciences and Medicine and a clinical professor of psychiatry and behavioral sciences, was part of the Clinical Neuroscience Internship Experience, or CNI-X, a weeklong immersion in the clinical and scientific research taking place in the Department of Psychiatry and Behavioral Sciences. More than 100 high school students from around the country attended the program this summer on the Stanford campus.

"With CNI-X, our faculty are taking the most direct route to the future — by introducing incredibly bright, motivated young people to the excitement and diversity of clinical neuroscience," said program co-director Laura Roberts, MD, MA, professor and chair of psychiatry and behavioral sciences, and chief of the psychiatry service at Stanford Health Care. "We introduce novel science to the interns, and they drive the discussion forward and yet also move quickly to issues of social justice and humanity. My guess is that in several years we will see some of these students in our medical school classrooms."

Students participated in sessions on topics ranging from the neuropsychiatry of HIV to molecular genetics, forensic psychiatry, eating disorders, hoarding and virtual-reality therapeutics. Class formats ranged from introductory seminars to hands-on workshops and laboratory tours.

"The program is designed to build early interest in medicine and psychiatry, destigmatize mental illness and spread knowledge about mental health," said CNI-X co-director Alan Louie, MD, professor and associate chair of psychiatry and director of education for the department. "Starting with high-school-age students also allows us to identify promising students interested in careers in mental health."

Launched in 2015

CNI-X launched last summer with 20 teens heading into their senior year. They participated in a week and a half of sessions. Most were interested in medicine, psychology, law, bioengineering and other fields. Louie said he hoped that what they learned during the program would inform their future careers.

"There are not many programs like this being offered, and apparently there's tremendous interest," said Louie. "It benefits everyone when people are better informed about mental health."

This year Louie and Roberts tweaked and expanded the CNI-X program, and 113 teens from throughout the Bay Area and as far away as Georgia, New York, Wyoming, Texas and Maryland, signed up. There were so many that they were broken into four groups, with classes repeated over two weeks to retain a small-group learning experience.

"I learned so much about neuroscience — I had no idea there were so many See NEUROSCIENCE, page 7

Surgeries found to increase risk of chronic opioid use, study finds

By Tracie White

A study of health insurance claims showed that patients undergoing 11 of the most common types of surgery were at an increased risk of becoming chronic users of opioid painkillers, according to researchers at the School of Medicine.

But the slight overall increase in risk of 0.5 percent in no way suggests that patients should skip surgery over concern of becoming addicted to opioids, the study said. Instead, it's a reminder that surgeons and physicians should closely monitor patients' use of opioids after surgery — even patients with no history of using the pain-relieving drugs — and use alternate methods of pain control whenever possible.

The study was published today in *JAMA Internal Medicine*.

"For a lot of surgeries there is a higher chance of getting hooked on painkillers," said the study's lead author, Eric Sun, MD, PhD, an instructor in anesthesiology at Stanford. Sean Mackey, MD, PhD, professor of anesthesiology, is the senior author of the study.

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The researchers examined the risks of chronic opioid use following 11 common types of surgeries. Chronic opioid use was defined in the study as patients who filled 10 or more prescriptions or received more than a 120-day supply of an opioid in the first year following surgery, excluding the first three months after surgery.

Patients who had knee surgery had the largest See OPIOID, page 6

First-ever restoration of vision achieved in mice, study says

By Bruce Goldman

Experiments conducted under the leadership of a School of Medicine investigator have succeeded, for the first time, in restoring multiple key aspects of vision in mammals.

In experiments in mice described in a study published online today in *Nature Neuroscience*, the scientists coaxed optic-nerve cables, responsible for conveying visual information from the eye to the brain, into regenerating after they had been completely severed, and found that they could retrace their former routes and re-establish connections with the appropriate parts of the brain.

That unprecedented, if partial, restoration could pave the way to future work that enables blind people to see.

The animals' condition prior to the scientists' efforts to regrow the eye-to brain-connections resembled glaucoma, the second-leading cause of blindness after cataracts. Cataracts can often be surgically removed, but there's no cure for glaucoma, said the study's senior author, Andrew Huberman, PhD, an associate professor of neurobiology. Jung-Hwan Albert Lim, a graduate student at the University of California-San Diego, is the lead author.

Glaucoma, caused by excessive pressure on the optic nerve, affects nearly 70 million people worldwide. Vision loss due to See RETINA, page 7

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Cheap blood test can discriminate between bacterial, viral infections

By Jennie Dusheck

Researchers at the School of Medicine have made an important breakthrough in their ongoing efforts to develop a diagnostic test that can tell health-care providers whether a patient has a bacterial infection and will benefit from antibiotics.

The study was published July 6 in *Science Translational Medicine*.

Antibiotics have saved millions of lives and created a world in which complex and lifesaving surgeries are possible. But the overuse of antibiotics threatens to create a global scourge of antibiotic-resistant bacterial pathogens. Because of this problem, public health experts regularly remind physicians to prescribe antibiotics only for bacterial infections. But too often there's no easy way for doctors to tell whether a patient's illness is bacterial or viral or, sometimes, if there's any infection at all.

"A lot of times you can't really tell what kind of infection someone has," said Timothy Sweeney, MD, PhD an engineering research associate with the Stanford Institute for Immunity, Transplantation and Infection and lead author of the paper. "If someone comes into the clinic, a bacterial or a viral infection often look exactly the same."

"The idea to look for a diagnostic test came from our previous paper in *Immunity* last year," said assistant professor of medicine Purvesh Khatri, PhD, the senior author. "In that paper, we found a common response by the human immune system to multiple viruses that is distinct from that for bacterial infections. We wondered whether we could exploit that difference to improve the diagnosis of bacterial or viral infections. But we needed a gene signature consisting of far fewer genes for the test to be clinically useful."

Blood test

The team used publicly available patient gene expression data to pinpoint just seven human genes whose activity changes during an infection; their pattern of activity can distinguish whether an infection is bacterial or viral.

When pathogens infect the cells of the body, the infection sets off a chain reaction involving the immune system that changes the activity, or expression, of hundreds of genes. Gene expression is the process by which cells extract information from genes and render it in the form of either proteins or RNA. Cells have the capacity to express more or less of each molecule, creating a pattern of gene expression that changes in response to external influences, including infections.

The seven-gene test is a vast improvement over earlier tests that look at the activity of hundreds of genes, the researchers said. Because so few genes are involved, the new test will be cheaper and faster, while remaining accurate, they said.

A study in Nepal co-authored by assistant professor of medicine Jason Andrews, MD, revealed that only 5 percent of patients who received antibiotics actually needed them, said Khatri. The Nepalese patients got antibiotic treatment because the drug was cheaper than trying to figure out if they actually needed it. "If we really want to make a difference," Khatri said, "our test has to be more cost-effective than the drug itself." That's an important breakpoint, he said, since it could allow health-care systems to use antibiotics appropriately and save money at the same time.

The work is part of a global response to the need to reduce the use of antibiotics, driven in part by President Obama's National Action Plan for Combating Antibiotic-Resistant Bacteria. Today, drug-resistant bacteria cause 2 million illnesses and 23,000 deaths each year in the United States alone, according to the Centers for Disease Control and Prevention. And, of the 154 million antibiotic prescriptions written in U.S. doctors' offices and emergency departments each year, it's estimated that 1 in 3 are unnecessary. A 2014 review of antimicrobial resistance reported that unless something is done to stop the evolution of antibiotic-resistant bacteria, such so-called superbugs could cost the world $100 trillion in gross-domestic-product losses by 2050.

NORBERT VON DER GROEBEN

Purvesh Khatri and his colleagues used publicly available patient gene expression data to pinpoint just seven human genes whose activity changes during an infection.

Finally, besides promoting the evolution of drug-resistant microbes, antibiotics increase the risk of side effects such as tendon rupture or kidney damage, and can damage gut and other microbiomes that are essential to overall health.

Hurdles ahead

The new gene-expression test for bacterial infection faces two hurdles before it can be made available to doctors in a few years. First, it must be thoroughly tested in a clinical setting. Until now, the data and test results for this ongoing work have all come from preexisting, online digital data sets of gene expression from patients with different kinds of infections — not from current patients.

The new study tested the seven-gene test on blood samples from 96 critically ill children and found that the test was accurate. But it needs to be further validated in larger numbers of patient blood samples, the researchers said.

Second, the test needs to be incorporated into a device that can give a result in an hour or less. The preliminary version of the blood test takes four to six hours — too long for people who are seriously ill. In patients who have sepsis, for example, the risk of death goes up by 6 to 8 percent for every hour that antibiotics are delayed, so it's critically important to act quickly.

In someone who is obviously severely ill, said Sweeney, prescribing antibiotics would be the default. But often patients have early bacterial infections and doctors don't yet realize the patient is in danger. The gene expression test could remove doubt in a matter of minutes, allowing doctors to prescribe antibiotics sooner and save lives.

For that reason, Sweeney and Khatri are working with other researchers on a way to engineer the gene expression test to provide results in under an hour. The plan is to combine an 11-gene test they created a few months ago with the more recent seven-gene test. The 11-gene test reveals if the patient has an infection at all. If they do have an infection, the seven-gene test reveals if it is bacterial or viral. Both tests would be run at the same time.

The researchers envision the two tests as a decision tree. "When you put the new seven-gene set together with the 11-gene set, we can make a decision tree that matches how a physician might think about a patient," said Sweeney. "First we ask, 'Is an infection present?' Because some people present with an inflammation, a fever, a high heart rate, but it's not due to an infection. Then we ask, 'If so, what kind?'"

The 18-gene combination test would first be used in hospitals, Sweeney said. It's possible, he said, that an even cheaper test just using the seven genes could be used in outpatient clinics.

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

Hector Wong, MD, of the University of Cincinnati College of Medicine, was another co-author of the study.

This research was supported by the National Institutes of Health, the Bill and Melinda Gates Foundation, a Stanford Child Health Research Institute Young Investigator Award (through the Institute for Immunity, Transplantation and Infection), and the Society for University Surgeons.

Stanford's Department of Medicine also supported the work.

The seven-gene set and the integrated antibiotics decision model have been disclosed by Sweeney and Khatri for possible patent protection to the Stanford Office of Technology Licensing. **ISM**

Stanford Cancer Institute earns highest cancer center designation

By Michael Claeys

The Stanford Cancer Institute has been designated a Comprehensive Cancer Center by the National Cancer Institute, a part of the National Institutes of Health and the world's leading cancer research organization.

The designation is recognition of the institute's robust and integrated programs encompassing laboratory research, clinical care and community outreach and education.

The institute's mission is to support and coordinate the wide range of cancer-related activities — in basic, translational, clinical and population-based science — occurring at Stanford University, Stanford Health Care and Lucile Packard Children's Hospital Stanford, along with its partner institution, the Cancer Prevention Institute of California. Its nearly 400 members include scientists and physicians from a wide range of disciplines, all collaborating to translate research advances into improved cancer treatments.

Building from a base of exceptional discovery research and patient care, the institute achieved its initial NCI "cancer center" designation in 2007, and in less than eight years has expanded its reach and its programs to earn the coveted "comprehensive" status.

"I want to recognize Dr. Beverly Mitchell, who has worked tirelessly since becoming the SCI director in 2008 to achieve this prestigious honor for Stanford Medicine," said Lloyd Minor, MD, dean of the School of Medicine. "The combined effort of the institute's multidisciplinary membership exemplifies how we are applying precision health to complex diseases and improving patient outcomes."

The leadership and dedication of faculty from a variety of scientific disciplines, combined with extraordinary institutional and community support, has positioned the institute for continued growth and achievement in the future, according to the NCI officials who visited Stanford and reviewed its application for "comprehensive" status. The NCI's site review summary noted that the institute "is clearly poised to make significant contributions to cancer research in the next five years."

"This achievement is a testament to the talent and dedication of our members," said Beverly Mitchell, MD, director of the Stanford Cancer Institute and a professor of medicine. "Our faculty and staff work together every day to improve the understanding and treatment of cancer, and to reduce its burden on patients and families."

In partnership with Stanford Health Care and Stanford Children's Health, the institute has undertaken a broad effort to transform the cancer patient experience by blending Stanford science with new models of patient care that incorporate concern for the psychological welfare of patients and families. This initiative is aimed at providing exceptional cancer care and improving the lives of patients. **ISM**

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STANFORD MEDICINE

Group of rare blood cancers responds to new drug treatment

By Krista Conger

A global trial of an oral medication called midostaurin indicates that the drug can produce partial or complete resolution of organ damage in 60 percent of patients with a group of rare blood cancers known collectively as advanced systemic mastocytosis.

The results of the open-label, phase-2 trial were published June 30 in the *New England Journal of Medicine*. Jason Gotlib, MD, an associate professor of medicine at the School of Medicine, led a team of international investigators that conducted the study, which enrolled 116 patients at 29 sites around the world. The study was funded by Novartis Inc., which manufactures midostaurin, also known as PKC412.

"Few patients with advanced systemic mastocytosis respond to the currently available drugs," said Gotlib. "They desperately need an alternative treatment. We are very hopeful that midostaurin will soon be approved by the FDA for this rare disease." Patients with advanced SM have a poor prognosis, with an expected life span of less than six months to 3.5 years, depending on the disease subtype.

Gotlib is the lead author of the study; Andreas Reiter, MD, of the University of Heidelberg, is the senior author.

Proliferation of mast cells

Systemic mastocytosis is caused by the abnormal accumulation of a type of white blood cell called a mast cell in the bone marrow, spleen, liver, lymph nodes, skin and gut. These cells mediate the body's allergic and inflammatory responses and play a role in defending the body against bacteria, fungi and viruses. Patients with systemic mastocytosis can experience flushing, itching, diarrhea and, in some cases, anaphylaxis, when the mast cells release inflammatory mediators such as histamine. In advanced forms of the disease, the infiltration of organs by the mast cells leads to low blood counts and liver function abnormalities as well as malabsorption and weight loss.

About 90 percent of patients with advanced SM have a particular mutation known as D816V in the gene that encodes a protein called KIT that controls the growth of mast cells. KIT is a member of a class of proteins called tyrosine kinases that modulate the activity of many signaling pathways within a cell. Mutations that cause kinases to be "always on" are responsible for many types of cancers, including advanced SM. Drugs known as protein kinase inhibitors are often used to block the activity of the mutated kinases in order to slow or stop disease progression.

However, the only currently approved treatment for advanced SM, a kinase inhibitor marketed by Novartis as imatinib, or Gleevec, is not active against the KIT protein with the D816V mutation — leaving most patients without an effective treatment.

Lack of options

Gotlib, a hematologist, pioneered the testing of midostaurin for advanced SM after becoming frustrated with the lack of treatment options.

In 2002, as a hematology fellow at Stanford, he treated a patient who was severely ill with another type of blood cancer caused by a mutated tyrosine kinase. The patient initially responded to imatinib, but developed another mutation in his cancer cells within a few months that led to resistance to the drug. Although Gotlib was unable to save that patient, the experience remained with him.

Shortly thereafter, researchers at Harvard showed that the imatinib-resistant cancer that Gotlib's patient developed could be overcome by midostaurin in a mouse model of the disease.

"I wondered if midostaurin could work for other patients resistant to imatinib," Gotlib said. He realized that advanced SM might be a good disease in which to test the drug, given that the majority of patients suffering from it carry the mutated KIT D816V protein resistant to imatinib.

'A dramatic response'

"I didn't have any patients with advanced SM at the time, but another physician in my division was treating someone with mast cell leukemia, a highly fatal variant of systemic mastocytosis," Gotlib said. He convinced Novartis to allow him to give the patient midostaurin under the company's compassionate-use program. "We saw a dramatic response. The patient, who was near death, improved enough to be released from the hospital, go home and begin cooking meals again."

Jason Gotlib

Although the patient's disease was controlled for only a few months, the experience established the potential activity of midostaurin in advanced SM. As a result, Gotlib, along with colleagues from Stanford and elsewhere, initiated further trials of midostaurin in the United States in 2005, as well as the current, international trial, which was launched in 2009.

Study findings

Sixty percent of patients in the current trial experienced complete or partial resolution of organ damage related to the disease. As a result, responding patients were less likely to need red blood cell or platelet transfusions and they experienced improvements in liver function and fewer signs of malabsorption such as weight loss.

Patients treated with midostaurin who experienced improvement in organ damage or a significant decrease in the percentage of abnormal mast cells in the bone marrow survived significantly longer than those who did not demonstrate these responses. The median overall survival of patients was 28.7 months. The survival benefit among patients with a severe subtype of the disease called mast cell leukemia was particularly striking, according to Gotlib. Although most people succumb to this form of the disease within six months of diagnosis, the median overall survival of all midostaurin-treated mast cell leukemia patients was 9.4 months.

Of 39 patients whose spleen size was evaluated, nearly 80 percent saw a reduction in the enlargement that is a common feature of advanced SM that contributes to abdominal pain and decreased appetite.

The most frequent side effects of midostaurin were low-grade nausea, vomiting and diarrhea, which were usually responsive to administration of the drug with meals and anti-nausea medicines. Patients otherwise reported a significant improvement in disease-related symptoms and quality of life.

Midostaurin is currently available on a compassionate-use basis for patients with advanced SM. Gotlib said the investigators hope to evaluate its use in earlier-stage patients whose disease is unresponsive to conventional clinical approaches or to prepare more advanced-stage patients for a bone marrow transplant in an attempt to cure the disease.

"This is an evolution of a treatment that originated in 2002 with a patient with an entirely different disease," Gotlib said. "We hypothesized that midostaurin might work for patients with advanced SM, and that led to a case report and ultimately the current international trial. Our study represents more than a decade of work and collaboration between academia, the pharmaceutical industry, and the SM patient community, and we are very hopeful that it will lead to approval of a new treatment for this rare, devastating disease."

The Charles and Ann Johnson Foundation and Stanford's Department of Medicine also supported the work. ISM

Mary Leonard appointed chair of pediatrics

By Erin Digitale

Mary Leonard, MD, MSCE, professor of pediatrics and of medicine, has been appointed chair of the Department of Pediatrics at the School of Medicine and physician-in-chief at Lucile Packard Children's Hospital Stanford and Stanford Children's Health.

Leonard took over July 1 from Hugh O'Brodovich, MD, professor of pediatrics, who retired after holding the position since 2007.

"This is an exceptionally exciting time for Stanford pediatrics," Leonard said. "The growth of our clinical and research programs and the new initiatives in precision health are providing us with unprecedented opportunities to shape the future of pediatrics. The house staff, faculty and patients inspire me in my work every day, and it will be an honor and privilege to advocate on their behalf."

A 1989 graduate of the School of Medicine, Leonard returned to Stanford in 2014 after spending 25 years at the Children's Hospital of Philadelphia and the University of Pennsylvania, first as a resident and fellow and then as a faculty member.

"Dr. Leonard is an energetic, collaborative physician and researcher who cares deeply about improving the health and well-being of children everywhere," said Lloyd Minor, MD, dean of the School of Medicine. "She is committed to Stanford Medicine's vision of proactive and personalized health care and has been at the forefront of efforts to integrate precision health approaches and skills into our training programs."

Studying lifelong bone health

"Dr. Leonard invariably receives high praise from colleagues and trainees for her thoughtful leadership and inspiring vision for the future of pediatric research, education and patient care," said Christopher Dawes, president and CEO of Lucile Packard Children's Hospital Stanford and Stanford Children's Health. "I'm very pleased to welcome her to the role of physician-in-chief of our hospital and network."

Mary Leonard

At the Children's Hospital of Philadelphia, Leonard directed the Office of Clinical and Translational Research and was a senior scholar in the Center for Clinical Epidemiology and Biostatistics, where she developed strong track records as a researcher and a mentor to other scientists. Her research has focused on the effects of chronic diseases on nutrition, physical function and bone health throughout life.

In 2015, after returning to Stanford, Leonard was appointed associate dean of maternal and child health research, a position in which she directed the transdisciplinary child and maternal health research and training initiatives of the Stanford Child Health Research Institute. She also helped build interfaces between Stanford's pediatric and adult medical research to facilitate scientific investigations across the life span.

"Dr. Leonard is a distinguished investigator, an expert clinician and a respected mentor who embodies the academic and integrated mission of Stanford Medicine," Minor said. "We are excited that she is embarking on this new role."

Leonard is a member of the American Society of Clinical Investigation and the Society for Pediatric Research. ISM

Grant applications sought in areas of immunity, transplantation, infection

The Stanford Institute for Immunity, Transplantation and Infection is seeking grant proposals for research funding in the general areas of immunity, transplantation and infection.

The institute will give preference to grant applications that are interdisciplinary and that have a disease focus.

In particular, the institute seeks proposals that address new areas of pediatric and obstetric research, along with pressing issues in transplant tolerance, allergies, infectious diseases, autoimmunity, aging and new methods for analyzing blood samples and other clinical samples.

Faculty members with principal-investigator status are eligible for $50,000 seed grants; postdoctoral scholars, clinical fellows, research associates and instructors are eligible for $25,000 seed grants.

The deadline for submitting proposals is 5:30 p.m. July 27.

For more information, contact Michele King at 723-3084 or mking@stanford.edu. ISM

‘Guided chemo missiles’ target cancer cells, spare healthy ones

By Amy Adams

There’s a good, bad and ugly to cancer chemotherapy. The good is that the drugs do often effectively kill cancer cells. The bad is that the drugs also damage other quickly dividing cells in the body, causing side effects ranging from cosmetic, like hair loss, to disabling.

The ugly occurs when the drug dose needed to kill a tumor is more than what a person’s body can handle. This might happen if the tumor doesn’t have much of a blood supply and very little of the drug, which is delivered through the bloodstream, can get in. A dose high enough to infiltrate the tumor could be deadly to other cells in the body. Some recently approved therapies get around this problem using antibodies to deliver a drug directly to tumors, bypassing healthy cells and possibly overcoming some of the uglier aspects of cancer chemotherapy.

Jennifer Cochran

Now Jennifer Cochran, PhD, associate professor of bioengineering, has built on this antibody approach using an engineered protein rather than an antibody to direct the drug to the tumor. Although the two techniques are conceptually similar, the specialized protein has the potential advantage of being able to pass through the barrier that protects the brain, thereby being able to treat brain tumors. It is also smaller than the antibody and might be able to reach dense tumors with little blood supply.

“Antibodies can be limited for treating solid tumors because they are too big to penetrate well,” Cochran said. “The idea is that a smaller molecule could diffuse into the tumor better.”

The work was published in a series of papers in the June issue of *Molecular Cancer Therapeutics* and the June 15 issue of *Angewandte Chemie*.

Targeting cancer

Cochran’s idea originated with the knowledge that cancer cells, and the blood supply that feeds them, often produce particular molecules known as integrins on their surface. The goal of her team was to create an engineered protein that could latch tightly onto those integrins and be used as a drug delivery vehicle.

First, the team needed to engineer a protein to bind integrins. Cochran employed a technique called directed evolution to rapidly engineer millions of proteins and screen for the qualities she’s interested in. In this case, they started with a protein called knottin — so named for its knotlike shape — and used directed evolution to engineer a protein variant that would bind strongly to integrins.

The researchers then worked on two strategies for attaching chemotherapeutic drugs to the evolved knottin. One strategy — carried out in collaboration with Sutro Biopharma, and led by former postdoctoral scholar Nicolas Currier, MD, PhD, and bioengineering graduate student Shelley Ackerman — used a portion of an antibody to connect the drug to the knottin, mimicking antibody therapies that are already on the market, perhaps speeding the time it would take to get this therapy approved for patients. The team tested this approach in a lab dish and in mice with implanted human tumors, and in each case the knottin successfully delivered the drug to the tumor and killed the cancer cells.

A second approach, developed in collaboration with postdoctoral scholar Nick Cox, PhD, in the Stanford ChEM-H Medicinal Chemistry Knowledge Center, used a small chemical link to attach a chemotherapeutic drug directly to the knottin. The knottin-drug combination effectively killed breast, ovarian and pancreatic cancer cells in a lab dish. The targeted drug delivery was highly effective against cancer cells, including those that had developed a resistance to the drug alone.

“We found that when the drug was delivered by the knottin, its potency was greatly enhanced in treating highly resistant tumor cells, like those found in pancreatic cancer,” Cox said.

In both approaches, the knottin portion of these multipart compounds binds to integrins present at high levels on cancer cells, delivering the drug directly into the cancer cell and bypassing healthy cells. Once inside, the drug is released and kills the cell. Because the drug is less active when connected to the knottin and cannot get inside cells of the body that do not express integrins, this approach could significantly reduce side effects on other tissues and organs.

Building on the past

This isn’t the first time Cochran has taken advantage of knottin’s affection for cancer cells. In previous work her team had attached the engineered protein to a fluorescent dye that was visible by molecular imaging techniques. This dye-labeled knottin could seek out and attach to cancer cells in the brain and elsewhere in the body and make them visible to doctors, who often have a hard time detecting whether drugs are shrinking tumors.

That previous work gave Cochran and her team some useful information. First, they learned that the knottin can get past a barrier that protects the brain from many molecules. And second, they learned that the protein does seek out cancer cells rather than healthy tissue. If it didn’t, the imaging signal would show a blur of light rather than visibly highlighting tumors.

“We’ve shown that these knottins can pass the blood-tumor barrier so the hope is that we can use this to deliver chemotherapy to brain tumors,” Cochran said.

Cochran is collaborating with Michelle Monje, MD, PhD, assistant professor of neurology, and Gerald Grant, MD, associate professor of neurosurgery, with the support of seed grants from Stanford Bio-X and the Stanford Child Health Research Institute to test this approach on childhood brain tumors.

These two knottin-based therapies are a first step. “These studies showed that we could use these molecules to deliver drugs to tumors,” Cochran said. “What we still need to understand is which cancers it works best on and what is the best chemotherapeutic drug to use.”

She and her team are also still exploring which of the two approaches will be most effective. The antibody-based protein-drug combination is larger and therefore might not work its way into dense tumors, for example, but will remain longer in the body and thus might deliver more benefits over time. The other compound is smaller and could penetrate more effectively into tumors but will be cleared quickly from the bloodstream, possibly reducing its effectiveness.

AUNTSPRAY / SHUTTERSTOCK.COM

Latching chemotherapy drugs onto proteins that seek out tumors could provide an effective way of treating tumors in the brain or with limited blood supply.

Cochran is a member of Stanford Bio-X, the Child Health Research Institute, the Stanford Cancer Institute, Stanford ChEM-H and the Stanford Neurosciences Institute.

The work was supported by the National Institutes of Health, the Stanford Child Health Research Institute, Stanford Bio-X, Stanford ChEM-H, the National Science Foundation and the Anne T. and Robert M. Bass Endowed Fellowship in Pediatric Cancer and Blood Diseases.

Stanford’s Department of Bioengineering also supported the work. The department is jointly operated by the School of Medicine and the School of Engineering.

ISM

Ami Bhatt awarded $100,000 prize to pursue microbiome research in Africa

By Beth Duff-Brown

Studying the microorganisms that live in our gut is a relatively new field, one that has taken off in the last decade. It is estimated that half of the microbes that live in and around our gastrointestinal tract have yet to be discovered.

“This means there is a huge amount of this dark matter within us,” said Ami Bhatt, MD, PhD, an assistant professor of medicine and of genetics at the School of Medicine. Her lab is devoted to exploiting disease vulnerabilities by cataloging the human microbiome, the trillions of microbes living in and on our bodies.

“I think if we fast-forward to the impact of some these findings in 10 years, we’re going to learn that modifying the microbiota is a potent way to modulate health,” Bhatt said. “Humans are not only made up of human cells, but are a complex mixture of human cells and the microbes that live within us and among us — and these microorganisms are as critical to our well-being as we are to theirs.”

Bhatt now intends to take this research to Africa. She will work alongside collaborators at the University of Witwatersrand in Johannesburg and the INDEPTH Network, an international consortium of research institutions that gathers health and demographic data from about 20 low- and middle-income countries.

Ami Bhatt

She is this year’s winner of the Rosenkranz Prize for Health Care Research in Developing Countries. The $100,000 prize is awarded by Stanford Health Policy to promising young Stanford researchers who are investigating ways to improve health care in developing countries.

Multinational microbiome project

Bhatt intends to use the money to execute the first multinational microbiome research project focused on noncommunicable disease risk in Africa. The project intends to explore the relationship between the gut microbiome composition and body mass index in patients who are either severely malnourished or obese.

“As a rapidly developing continent with extremes of resource access, Africa is simultaneously faced with challenges relating to the extremes of metabolic status,” Bhatt wrote in her Rosenkranz project proposal. The Bay Area native, who is also the director of global oncology at Stanford, came to the School of Medicine in 2014 to focus on how changes in the microbiome are associated with cancer.

In this new project, Bhatt and members of her lab will team up with colleagues in South Africa, Ghana, Burkina Faso and Kenya. They will leverage the infrastructure already in place at the INDEPTH Network of researchers, using an existing cohort of 12,000 patients within those four countries. The patients have already consented to be involved in DNA testing and have given blood and urine specimens.

Identifying alterations of the microbiome that are associated with severe malnutrition or obesity could pave the way for interventions that may mitigate the severity or prevalence of these disorders, Bhatt said.

‘Critical to our health’

“These organisms are critical to our health in that they are in a delicate balance with one another and their human hosts,” she said. “Alterations in the microbiome are associated with various diseases but have mostly been studied in Western populations. Unfortunately, little is known about the generalizability of these findings to low- and middle-income countries, where most of the world’s population lives.”

Bhatt said that as Africa rapidly continues to develop, the continent is simultaneously faced with challenges relating to extreme weight gain and loss. While the wealthy are facing obesity and its associated diseases, such as stroke, heart failure and diabetes, many people are still faced with issues related to food insecurity, hunger and malnutrition.

The research, she hopes, could lead to aggressive behavioral, dietary and lifestyle modifications targeted at maintaining healthy BMI in at-risk individuals.

The award’s namesake, George Rosenkranz, who holds a doctorate in chemistry, first synthesized cortisone in 1951, and later progestin, the active ingredient in oral birth control pills. He went on to establish the Mexican National Institute for Genomic Medicine, and his family created the Rosenkranz Prize in 2009.

The award embodies Rosenkranz’s belief that young scientists hold the curiosity and drive necessary to find alternative solutions to longstanding health-care dilemmas. ISM

Physicians innovate to protect children's health in Guatemala

By Nicole Feldman

Stanford pediatrician Paul Wise, MD, MPH, stooped below the black tarp roof of a cinderblock house in Guatemala to offer his condolences to a mother who had just lost her child.

"Doctor Pablo," as he is known in the communities around San Lucas Tolimán, talked softly as he relayed his sympathies to the mother, whose 9-year-old son had been a patient of his.

The boy's genetic disorder would have been terminal anywhere, but thanks to Wise and local health promoters, the boy's family had years with him instead of months. They found the doctor through the Guatemala Rural Child Health and Nutrition Program, a collaboration between Wise and the health promoters to eliminate death by malnutrition for children under 5.

While Wise spoke to the heartbroken mother, his Stanford research assistant, Alejandro Chavez, helped the promoters set up inside a local community center to measure the weight and height of local kids to determine their nutrition level.

Chavez and the promoters had worked together for months to create an app for tablets that will make it easier to find malnourished children.

The app they designed will decrease training time for new health promoters and allow the program to expand. The goal is to distribute the app globally to help programs in other countries tackle malnutrition.

Children in crisis

As recently as 2005, about one of every 20 children in this rural area of Guatemala died before their fifth birthday. Almost half the deaths were associated with severe malnutrition.

"The death of any child is always a tragedy, but the death of any child from preventable causes is always unjust," said Wise, a Stanford Health Policy core faculty member and a professor of pediatrics at the School of Medicine.

Along with other faculty from the Freeman Spogli Institute for International Studies and the medical school, Wise created the Children in Crisis Initiative to improve the health of children in areas of the world plagued by conflict and political instability. The program brings together Stanford researchers and students across disciplines.

Nowhere are their efforts better illustrated than in the rural communities around San Lucas Tolimán, in the central mountains of Guatemala.

The program's effectiveness rests on a deep respect for the local communities merged with innovation by Stanford researchers.

"It's absolutely essential to any program that the people in need be part of the solution," said Wise, who is the Richard E. Behrman Professor of Child Health and Society. Unlike many nongovernmental organizations and health programs, Wise believes the way to create a sustainable health system is for the locals to run it, so the health promoters manage the program's day-to-day activities.

This leaves the Stanford team free to focus on innovation, such as the new app. They believe the technology could change child health programs around the world. Wise's team has partnered with Medic Mobile, a nonprofit that creates open-source software for healthcare workers, which plans to distribute the app to other areas suffering from malnutrition.

The six Android tablets purchased by Children in Crisis are enough to monitor the program's 1,500 kids through the app.

Role of nutrition

When done well, nutrition surveillance is very effective at decreasing child mortality in poor countries.

"Nutrition contributes enormously to health and well-being," Wise said as he walked through Tierra Santa, a small community near San Lucas, making house calls. "So the focus of our work turned to improving young child nutrition. It's not an easy thing to do in a place that's extremely poor."

Wise and his Stanford colleagues — medical student Victoria Bawel and associate professor of pediatrics Lisa Chamberlain, MD, MPH — made their rounds during their visit in March. Evidence of poverty was everywhere.

Here, clean tap water is a dream and even the sturdier homes often lack four walls or paned windows, though the children were neatly dressed in T-shirts or colorful *traje*, traditional Mayan clothing.

It's hard to provide proper nutrition when most families can't find enough work to buy adequate food. But a little help can make a big difference.

Bawel, a first-year medical student who plans a career improving health in areas of poverty, was struck by the impact the promoter program has had on the community.

"There are children who need supplements and nutrition to stay alive," she said. "Without this program, that infrastructure does not exist."

With FSI's assistance, the nutrition program distributes Incaparina, a supplement of cornmeal, soy and essential nutrients. The sweet, mealy drink helps the program's most malnourished children get back on track.

"I feel like they've been very honest with me about things I need to improve," he said.

Cesia Lizeth Castro Chutá is a senior coordinator for the program who has worked with Chavez to ensure that the app meets the promoters' needs.

NICOLE FELDMAN

First-year medical student Victoria Bawel plans a career improving health in areas of poverty. Through the Children in Crisis Initiative, children like Fátima are getting the nutritional supplements they need.

Every two months, the promoters gather each community's children to measure their weight and height. Children and their mothers sit patiently, waiting for their turn. The children enjoy a cup of Incaparina, and their mothers eagerly listen to the promoters' tips for keeping their children healthy.

"It's very important to me," said Elsira Rosibel Samayoa, who brought her 2-year-old to be measured. "There are mothers who don't understand the importance of monitoring their children's weight, but I do."

Since its implementation in 2009, the Stanford program has slashed nutrition-based mortality in the participating communities by about 80 percent and decreased severe malnutrition by more than 60 percent, saving hundreds of children's lives.

However, nutrition surveillance and intervention isn't easy. Tracking nutrition takes training and expertise, and when the local population rarely exceeds a fourth-grade education, learning these skills is especially challenging. Detailed graphs on a standard growth chart are essential to identifying malnourished children.

"The community health workers are extremely capable and smart, but some have never seen a graph before," said Wise. "Think about what it is to try to explain a graph to someone for the first time."

It takes the health workers about three years to learn to graph and then interpret the results for intervention.

Wise said, "So we all got together and said, 'How do we make this easier to do?'"

The app was the answer.

'Let's create an app'

Enter Alejandro Chavez, a recent Stanford computer science graduate and Stanford Health Policy research assistant. He developed the app, which helps users collect health data on children and then determines whether they are malnourished and need an intervention.

"The major goal was to lower training requirements and make programs like this simpler to start and maintain," said Chavez, who travels often to work in Guatemala, where he gets feedback from the health promoters.

"The tablet automatically generates the information we need to know," she said. "It becomes easier to confirm that a child is malnourished and needs supplements."

Looking forward

With the app's launch, it looks like training time for the promoters will be reduced from three years to less than six months. That means new communities can be incorporated into the program quickly, creating broader access to care.

Meanwhile, many health programs around the world are waiting to see how well the Stanford app works in Guatemala.

Josh Nesbit, a Stanford alumnus and Medic Mobile CEO, said, "As more health programs recognize the importance of nutrition and implement community-based interventions, screening and surveillance tools will be critical. We must learn from Dr. Wise's success." ISM

NICOLE FELDMAN

"Doctor Pablo," aka Stanford pediatrician Paul Wise, examines a boy in the community of Nueva Vida.

Three researchers receive awards to study epilepsy

Three Stanford researchers have received early-career awards from the American Epilepsy Society.

JULIET KNOWLES, MD, PhD, a chief resident in neurology, received an AES Research and Training Fellowship for Clinicians, which includes a $50,000 award to study the effect of recurrent seizures on myelin structure and plasticity.

MEGAN WYETH, PhD, a postdoctoral scholar in comparative medicine, received an AES Postdoctoral Research Fellowship, which includes a $45,000 award to study the inhibitions of interneurons in a model of temporal lobe epilepsy.

CHRISTOPHER MAKINSON, PhD, a postdoctoral scholar in neurology and neurological sciences, received an AES/Wishes for Elliott Postdoctoral Research Fellowship, which includes a $45,000 award to use a 3-D human culture platform to test therapies for a type of epilepsy caused by a genetic mutation known as SCN8A. ISM

Study describes how nanofiber scaffolds could treat lymphedema

By Sarah C.P. Williams

Researchers at the School of Medicine have developed a possible treatment for lymphedema, the severe swelling of an arm or leg that can occur when the lymph system is blocked. Using scaffolding composed of specially patterned collagen nanofibers, the researchers coaxed lymph vessels to grow around lymph blockages.

The technique was effective at treating lymphedema in pigs, the scientists report in a study published online June 7 in *Biomaterials*.

"We were able to take a cue from nature about what molecules spur vessel growth, but also think outside the box and use this nanoscale scaffolding to bridge the blockages," said Ngan Huang, PhD, assistant professor of cardiothoracic surgery and a co-senior author of the study. "I think combining the two was really key."

A disease without a cure

The lymphatic system is responsible for draining fluids from the body's tissues and filtering this lymph fluid. When a lymphatic vessel is blocked, as is the case in lymphedema, fluid can get backed up into a limb, causing painful swelling.

In developed countries including the United States, lymphedema is most often seen in cancer patients whose lymph nodes are affected by their cancer. But infections and genetic conditions can also cause lymph blockages. In some cases, the underlying cause of the disease — such as an infection — can be treated. But for many, physical therapy, massage and compression garments are the only options to treat the disease and provide just temporary relief.

"Lymphedema is a chronic, debilitating disease with profound functional and psychosocial implications," said Stanley Rockson, MD, professor of medicine and a co-senior author of the paper. "Current treatments are extremely limited. While transplantation of healthy lymph nodes represents a theoretically viable treatment option for cancer survivors and others, the success rate of these procedures has been disappointing."

Rockson holds the the Allan and Tina Neill Professorship in Lymphatic Research and Medicine.

Nano-braids

Huang's lab, in collaboration with the Union City, California-based company Fibralign, has been studying how nanofibers of collagen can be used in medicine. Collagen, the most abundant protein in the human body, acts as a structural support in a variety of tissues. The scientists have designed nanofibers, dubbed "BioBridge," that mimic collagen's different arrangements.

"The unique feature about the BioBridge scaffolds is that they're not just noodles on a nanoscale," said Huang. "They have patterning that's physiologically relevant." The scaffolds used in the recent work, she said, look like braided noodles, and mimic how collagen is naturally arranged in some connective tissues in the body. The threadlike fibers are each about a third of a millimeter wide.

Previously, Huang's group has studied how the BioBridge nanofibers can be used to guide new blood vessels. As new cells that make up the vessels grow, they align themselves along the nanofibers. But lymph vessels, at a molecular level, are similar to blood vessels. So Huang and her collaborators wondered whether the fibers could also be used to coax and direct new lymph vessel growth as well.

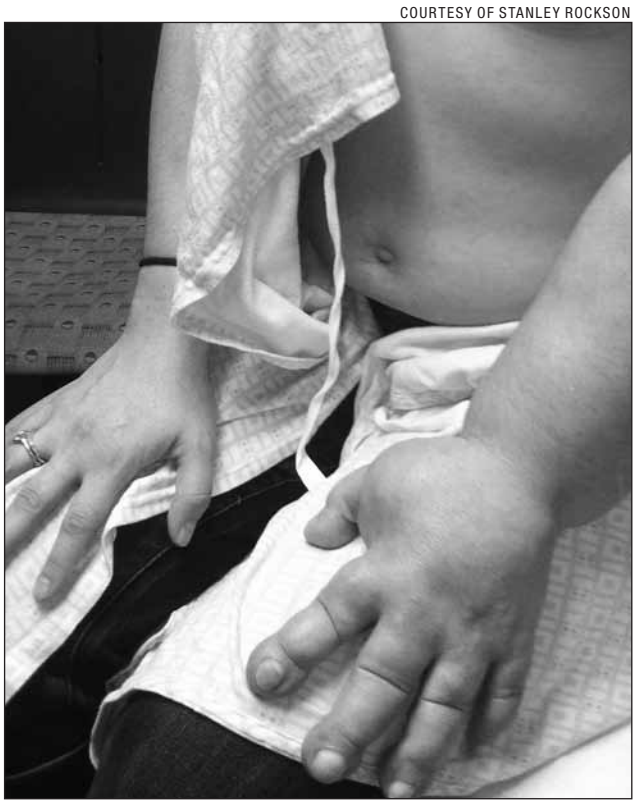
Bridging lymph blockages

The scientists coated stretches of the BioBridge nanofibers with fragments of lymph nodes, since the nodes are known to produce molecules that stimulate new lymph vessel growth. Then, they surgically implanted the fibers around lymph blockages in pigs with lymphedema, building a stretch of fibers that bypassed each blockage like a bridge. After three months, the eight pigs that had received BioBridge scaffolding had 27 lymphatic collector vessels per square millimeter in the area around the implant, significantly more than the 1 lymphatic collector per square millimeter seen in control animals. Moreover, animals with the nanofibers had reduced fluid buildup in their limb affected by lymphedema.

Ngan Huang

"The sample size wasn't as good as we would eventually like, but we followed these animals for a total of six months and got a lot of safety data," said Huang. "There weren't any adverse events."

COURTESY OF STANLEY ROCKSON



The lymphatic system drains fluids from the body's tissues. When a lymphatic vessel is blocked, as is the case in lymphedema, fluid can get backed up into a limb, causing painful swelling.

Moving to humans

So far, the BioBridge approach has only been tested in pigs. But Fibralign has a small clinical trial planned in Latin America, and Rockson is putting together a Stanford-based study to test the treatment in breast cancer patients with lymphedema.

The lead author of the paper is Catarina Hadamitzky, MD, of the Helios Clinic in Hildesheim Germany. The other co-senior author is John Cooke, MD, PhD, formerly a professor of medicine at Stanford who is now at the Houston Methodist Research Institute in Texas.

Other Stanford co-authors are former postdoctoral scholar Magdalena Bazalova-Carter, PhD; postdoctoral scholar Luqia Hou, PhD; research associate Yuka Matsuura; assistant professor of medicine Rajesh Dash, MD, PhD; and associate professor of medicine Phillip Yang, MD. They collaborated with researchers from the University of Victoria, Veterans Affairs Palo Alto Health Care System, Surpass Inc., IntraOp Medical Corp. and Fibralign Corp., which produces the aligned nanofibrillar collagen scaffolds used in this study. Hadamitzky and Cooke have received subscription rights in Fibralign.

The study was funded by the U.S. Army Medical Research & Materiel Command and the National Science Foundation.

Stanford's Department of Cardiothoracic Surgery also supported the work. ISM

Opioid

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risk, as they were roughly five times more likely than a control group of nonsurgical patients to end up using opioids chronically, followed by those undergoing gall bladder surgery, whose risk was three-and-a-half times greater than those in the control group.

"We also found an increased risk among women following cesarean section, which was somewhat concerning since it is a very common procedure," adding that the risk was 28 percent higher than among the control group, Sun said.

Other factors that contributed to an increased risk for chronic opioid use included being male, elderly, taking antidepressants or abusing drugs.

The opioid abuse epidemic

Since prescription painkillers became cheap and plentiful in the mid-1990s, drug overdose death rates in the United States have more than tripled, according to the Centers for Disease Control and Prevention. Seventy-eight Americans die every day from an opioid overdose, it reported.

Previous studies have shown increased risks of chronic opioid use post-surgery, but unlike past studies, Sun and colleagues set out to examine patients who hadn't received prescriptions for opioids for at least one year prior to surgery. Among the opioid prescription drugs examined in the study were hydrocodone, oxycodone and fentanyl — the drug responsible for the recent accidental overdose death of legendary musician Prince.

The researchers examined health claims from 641,941 privately insured patients between the ages of 18 and 64 who had not filled an opioid prescription in the year prior to surgery, then compared them with about 18 million nonsurgical patients, who also hadn't received opioid prescriptions for at least a year. The claims were filed between 2001 and 2013 and provided by Marketscan, a database of 35 million beneficiaries.

Except for the minor procedures known to be somewhat pain-free, such as a cataract surgery and laparoscopic appendectomy, all 11 types of surgery were associated with an increased risk of chronic opioid use, the study said.

Eric Sun

Other pain-control measures

"The message isn't that you shouldn't have surgery," Sun said. "Rather, there are things that anesthesiologists can do to reduce the risk by finding other ways of controlling the pain and using replacements for opioids when possible."

> "The message isn't that you shouldn't have surgery."

Sun said he and his colleagues in surgery and anesthesia at Stanford try to use regional anesthetics when possible to reduce the need for opioids post-surgery. He added that patients should also be encouraged to use pain-management alternatives such as Tylenol following surgery.

"Even when taken exactly as prescribed, opioids carry significant risks and side effects," said study co-author Beth Darnall, PhD, clinical associate professor of anesthesiology and author of the book Less Pain, Fewer Pills: Avoid the Dangers of Prescription Opioids and Gain Control over Chronic Pain. "Ideally, opioids are avoided in treating chronic pain, and pain treatment should emphasize comprehensive care, including physical therapy, pain psychology and self-management strategies."

As a pain psychologist and clinician-scientist, Darnall emphasizes alternate methods of pain management based on evidence-based techniques that can help calm the nervous system such as diaphragmatic breathing, progressive muscle relaxation and mindful meditation.

She is studying the use of a pain psychology class at Stanford for women undergoing surgery for breast cancer called "My Surgical Success" designed to help patients develop a personalized pain-management plan to control the anxiety associated with anticipating surgical pain.

"It turns out that a lot of chronic pain develops from surgery, and pre-surgical pain 'catastrophizing' is a major risk factor for having a lot of pain," Darnall said. "We hope that by optimizing patients' psychology — and giving them skills to calm their own nervous system — they will have less pain after surgery, need fewer opioids and recover quicker."

Laurence Baker, PhD, professor of health research and policy, is also a co-author of the paper.

The research was funded by a grant from the Foundation for Anesthesia Education and Research and the Anesthesia Quality Institute.

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

Neuroscience

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subspecialties," said Houston native Ananya Venkat, 17, who was staying with relatives who lived nearby. "I was not considering medical school before, but this internship elucidated things for me. The brain is so complex."

Entertaining and educational

Pelayo was one of 25 department faculty members who volunteered to teach a 90-minute class four times over the two weeks. "Many of my adult patients trace the beginning of their sleep problems to adolescence. The societal pressure to sleep less has been increasing across all age groups, and it has health consequences that have been largely ignored," he said. "Teenagers are very receptive to learning how their brain works, and sleep and dreams are topics they are particularly drawn to."

Classes were formulated to be entertaining as well as educational. Participants got to try on virtual reality headsets, watch zebrafish populations used in genetic studies, observe videos of brain cell development and barter personal items to role-play hoarding behavior.

NORBERT VON DER GROEBEN

Kendall Look of Los Altos, Muhammad Dhanani of Atlanta and Ananya Venkat of Houston were among the more than 100 students who participated in the Clinical Neuroscience Internship Experience this summer.

"We wanted the experience to address issues that are important and relevant to teens and present topics appropriate to their knowledge level," Louie said.

One session, for example, represented symptoms of psychosis by having two students converse while a third whispered in one's ear. The exercise is designed to build empathy by illustrating the distraction of hearing voices, said Kate Hardy, DClinPsy, clinical assistant professor of psychiatry and behavioral sciences.

"Some students said they found it hard to concentrate; others said the experience was scary or threatening. When I do this exercise with adults, it's difficult to get them to respond. The teens got right into it," Hardy said. "There's a great benefit to exposing people at that age to the prevailing preconceptions of psychosis and reduce the stigma, even at a small scale."

In another session, students observed Lawrence McGlynn, MD, clinical professor of psychiatry and behavioral sciences, with a patient who had volunteered to share the experience of living with a stigmatizing condition. "The students were extraordinarily touched by the interaction and seeing the importance of a therapeutic relationship," McGlynn said. "They showed tremendous respect and kindness during this session, which touched us all."

NORBERT VON DER GROEBEN

Psychiatrist Alan Louie teaches a class titled "Constructing the Human Brain."

Sustaining students' attention

Pelayo said that the length of the classes allowed both teachers and students to delve more deeply into specific subjects. "Most high schools do not have 90-minute class sessions because it can be difficult to sustain their attention for that long," he said. "Yet we could have gone much longer because sleep is a topic that is not covered in the school curriculum, and they understand that it affects them directly."

> "It benefits everyone when people are better-informed about mental health."

Students worked in teams to present a capstone project at the end of the program that incorporated lessons learned and personal interests. One team designed an app to warn caregivers in multiple languages when an Alzheimer's patient is wandering. Another group created a Snapchat account with videos and stories about schizophrenia, using a first-person approach to educate users about the disorder. Another team presented a plan to create a website buddy system for caregivers of autistic children. Teams also gave presentations on whether music enhances cognitive processing, the difficulty of advocating for services for students with ADHD in schools and social and economic disparities in serious mental illness.

"I've learned so much, and it's helped me to shift my career focus," said Sachin Jaishankar, 15, who was also volunteering at hospitals in his home state of Arizona over the summer. "I wanted to spend part of my summer in a university learning environment, and now I'm definitely interested in shifting my focus to clinical neuroscience." ISM

Retina

continued from page 1

optic-nerve damage can also accrue from injuries, retinal detachment, pituitary tumors, various brain cancers and other sources.

Thin sheet of cells

The retina, a thin sheet of cells no more than half as thick as a credit card, is the light-sensing part of the eye. If nerve cells were offices, this tiny patch of tissue would be Manhattan. Photoreceptor cells in the back of the retina react to different wavelengths of light by sending electrically coded information to other cells in the retina called retinal ganglion cells, of which there are as many as 30 types, each specializing in processing a particular aspect of vision, such as upward motion, motion in general or the color red. The ganglion cells project long, electric-wire-like processes called axons, which extend down the optic nerve in a bundle and then fan out to numerous regions of the brain, where they connect with other nerve cells to inform them about the visual world.

Andrew Huberman

"Somehow the brain can interpret these electrical signals to say, 'Wow, that's a fast-moving car coming my way — I'd better get back on the sidewalk,'" said Huberman.

"More than a third of the human brain is dedicated to the processing of visual information," he said. "Over two dozen brain areas get direct signals from retinal ganglion cells. These areas are involved in not only what we typically think of as vision, but also circadian rhythms and mood."

Retinal ganglion cells are the only nerve cells connecting the eye to the brain, said Huberman. "When those cells' axons are severed, it's like pulling the vision plug right out of the outlet," he added.

Axons in eye don't regenerate

When axons in the brain and spinal cord of a mammal such as a mouse or a human have been damaged, they don't regenerate on their own. (The only known exception is olfactory sensory nerve cells.) The retina, too, is actually part of the brain, said Huberman. Damage to mammalian retinal ganglion cells' axons spells permanent vision loss.

Mammalian axons located outside the central nervous system do regenerate, though. And during early development, brain and spinal-cord nerve cells abundantly sprout and send forth axons that somehow find their way through a thicket of intervening brain tissue to their distant targets. In a full-grown adult human, the axons snaking from retinal ganglion cells to one distant brain structure called the superior colliculus can reach 6 to 8 inches in length.

While many factors are responsible for adult brain cells' lack of regenerative capacity, one well-studied cause is the winding down, over time, of a growth-enhancing cascade of molecular interactions, known as the mTOR pathway, within these cells.

In the study, adult mice in which the optic nerve in one eye had been crushed were treated with either a regimen of intensive daily exposure to high-contrast visual stimulation, in the form of constant images of a moving black-and-white grid, or biochemical manipulations that kicked the mTOR pathway within their retinal ganglion cells back into high gear, or both. The mice were tested three weeks later for their ability to respond to certain visual stimuli, and their brains were examined to see if any axonal regrowth had occurred.

Importantly, while retinal ganglion cells' axons in the crushed optic nerve had been obliterated, the front-line photoreceptor cells and those cells' connections to the retinal ganglion cells in the damaged eye remained intact.

Success of combined approach

While either visual stimulation or mTOR-pathway reactivation produced some modest axonal regrowth from retinal ganglion cells in mice's damaged eye, the regrowth extended only to the optic chiasm, where healthy axons exit the optic nerve and make their way to diverse brain structures. But when the two approaches were combined — and if the mouse's undamaged eye was temporarily obstructed in order to encourage active use of the damaged eye — substantial numbers of axons grew beyond the optic chiasm and migrated to their appropriate destinations in the brain.

"Somehow these retinal ganglion cells' axons retained their own GPS systems," Huberman said. "They went to the right places, and they did not go to the wrong places."

> "Somehow these retinal ganglion cells' axons retained their own GPS systems."

Tests of the mice's vision indicated that visual input from the photoreceptor cells in their damaged eye was reaching retinal ganglion cells in the same eye and, crucially, being conveyed to appropriate downstream brain structures essential to processing that visual input. One test, for example, involved the projection of an expanding dark circle — analogous to a bird of prey's approach — onto the visual field of the damaged eye. In response, most of the mice subjected to both mTOR-pathway upregulation and visual stimulation, as well as obstruction of their remaining good eye, did what they would be expected to do in the wild: They headed for the shelter of a "safety zone" in the experimental set-up.

In other words, the regenerating axons, having grown back to diverse brain structures, had established functional links with these targets. The mice's once-blind eye could now see.

Restored vision incomplete

However, even mice whose behavior showed restored vision on some tests, including the one described above, failed other tests that probably required finer visual discrimination, said Huberman. He noted that the investigators could prove that axons from two specific retinal ganglion cell types had reached their targets, but lacked molecular labels that would have let them determine whether axons emanating from the rest of the other subtypes had done so. Further progress, he suggested, will depend on boosting total numbers of retinal ganglion cell axons that successfully extend back to and establish former contact with their target structures, as well as finding ways to engage and assess most or all of the roughly 30 subtypes of retinal ganglion cells.

"We're working on that now," Huberman said.

The study was conducted in collaboration with researchers at UCSD, Harvard University and Utah State University.

Funding for the study was provided by the National Eye Institute and the Glaucoma Research Foundation.

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

Study: Exposure to hormone disruptor linked to canned food

By Rob Jordan

A new study by researchers at Stanford and Johns Hopkins universities puts to rest any lingering doubt about whether eating canned food increases exposure to a chemical linked to diabetes, cardiovascular disease and other health effects.

The research, a first-of-its-kind national sample, also highlights specific canned foods linked to higher levels of the chemical Bisphenol A, or BPA.

The study, published online June 29 in *Environmental Research*, highlights the challenges consumers face in trying to limit their exposure to BPA, a compound used to make, among other things, resins that coat the inside of food cans and jar lids. Different foods have different amounts of BPA contamination.

EVLAKHOV VALERIY / SHUTTERSTOCK

"I could eat three cans of peaches, and you could eat one can of cream of mushroom soup and have a greater exposure to BPA," said lead author Jennifer Hartle, PhD, postdoctoral scholar at the Stanford Prevention Research Center at the School of Medicine.

Previous research has focused on analyzing levels of BPA in canned products and measuring BPA exposure within groups of fewer than 75 people. Evaluating both dietary sources of BPA contamination and BPA levels in the urine of people who recently consumed canned food, the new analysis assessed thousands of people of various ages and geographic and socioeconomic backgrounds.

Urinary BPA concentrations

Hartle and her colleagues found that canned food was associated with higher urinary BPA concentrations, and the more canned food consumed, the higher the BPA. The result confirms canned food's outsized influence on exposure to BPA. The researchers also found that particular kinds of canned food were associated with higher urinary BPA concentrations. The worst offenders (in descending order): canned soup, canned pasta, and canned vegetables and fruit.

Jennifer Hartle

A previous study led by Hartle found that children, who are especially susceptible to hormone disruption from BPA, are at risk from school meals that often come from cans and other packaging. This uptick in packaging is a result of schools' efforts to streamline food preparation and meet federal nutrition standards while keeping costs low.

In 2015, as part of the Stanford Woods Institute for the Environment's Rising Environmental Leaders Program, Hartle met with members of Congress who are working on regulating BPA in food packaging.

California has listed BPA as a female reproductive toxicant, and the U.S. Food and Drug Administration has restricted its use in some products. However, the FDA is still working to "answer key questions and clarify uncertainties about BPA," according to the agency's website.

"The FDA no longer allows BPA to be used in baby bottles, sippy cups and liquid infant formula canned linings, and many food and beverage companies are moving away from the use of BPA," Hartle said. "However, we do not know if synthetic BPA replacements are safe either."

The researchers suggest that federal regulators expand testing beyond BPA to other chemicals used as BPA replacements in food packaging, none of which are included in national monitoring studies.

Co-authors of the study include Ana Navas-Acien of Johns Hopkins and Columbia universities, and Robert Lawrence of Johns Hopkins. **ISM**

22-year-old patient marks five years of living with mechanical heart pump

By Melissa Schenkman

When people meet Edgar Arredondo, 22, of Newark, California, they are immediately drawn to his easygoing nature, his positive outlook on life and his unfailing smile. An aspiring graphic designer who has battled Becker muscular dystrophy since elementary school, Arredondo prefers pursuits that allow him to take things at his own pace, tackling them the same way he has taken on the rest of life's challenges — all in stride.

It's an approach that continues to captivate his family, friends and the care team at Lucile Packard Children's Hospital Stanford Heart Center as he marks an extraordinary five years of living with a ventricular assist device attached to his heart. The device was implanted at Packard Children's in 2011. "What jumps out at me about Edgar is that he is able to maintain enthusiasm, positivity and grace, all at once, in the face of a series of medical challenges," said David Rosenthal, MD, director of the hospital's VAD program and professor of pediatrics at the School of Medicine.

Arredondo's personal milestone is also a record for the VAD program: He has been living on a VAD longer than any other pediatric recipient in the hospital's history, and possibly in the country. To mark this milestone, Arredondo and his family gathered recently in the hospital's courtyard along with dozens of people from his care team, past and present, including members who were on their day off and those who have retired but who wanted to return for the momentous occasion.

"Edgar, you have been an inspiration to all who have cared for you," said Daniel Bernstein, MD, the Alfred Woodley and Mabel Salter Endowed Professor in Pediatrics, who has been closely involved in Arredondo's care over the years.

Arredondo wore an ear-to-ear grin as he read aloud from a letter to his supporters, expressing his heartfelt gratitude to all who have helped him along his journey.

How it all began

Around age 6, a completely mobile Arredondo noticed that he felt tired when walking long distances and fell more often than his classmates.

"It was hard to keep up with the other kids," he said. "When I used to go up the stairs or curbs, it was really hard. Those muscles weren't as strong, I guess, so I couldn't do those things."

Arredondo's difficulty with movement was not just on his own radar. His mom and his teachers noticed, too.

At 9 years old, he had a muscle biopsy. He was diagnosed with Becker muscular dystrophy, a genetic disease that causes muscle breakdown and weakness. It typically affects muscles in the thighs, hips, shoulders and pelvic area.

Arredondo got around mostly by walking until he entered junior high, when he opted to use a wheelchair to navigate the campus. Other than that, the condition did not faze him. School was going well and he had a loyal group of friends. "They would include me in everything, even if I couldn't do anything," he said.

When he was a high school freshman, Arredondo's dystrophy began to show its unpredictable side. He felt very weak, had little appetite and often couldn't keep his food down.

After a series of tests, it was determined that the disease was affecting a very important muscle: his heart.

"With muscular dystrophy, you get a dilated cardiomyopathy, a weakness of the heart muscle that is in direct parallel to the skeletal muscle," Rosenthal said.

Arredondo was referred by Children's Hospital Oakland to Lucile Packard Children's Hospital Stanford, the only pediatric heart transplant center in Northern California.

It's a referral his family is very grateful for.

NORBERT VON DER GROEBEN

Edgar Arredondo, front, with his sisters, father and mother. Arredondo had a ventricular assist device implanted in his chest at Lucile Packard Children's Hospital Stanford.

"Becoming a patient at Stanford was a new opportunity for Edgar to have life," said Imelda Arredondo, Edgar's mother. "The doctors and nurses love their work. They worry not just about the patient, but the family, too. No matter your background they treat you good."

Ventricular assist device program

Mending poorly working hearts is nothing new for Packard Children's. For years, the program has been using medications and VADs to keep children's hearts functioning while they await a transplant.

Historically, life with a VAD has meant staying inside the hospital. Rosenthal and his team pioneered the use of durable VADs in kids, building the foundation for a treatment program that includes living at home and going to a mainstream school. The result for many patients is a higher quality of life.

"In 2010, we started using a VAD called the HeartMate 2, which is totally implanted in the body and has wires on the outside that are easier to care for," nurse practitioner Aileen Lin, RN, said. "Most places weren't trying this in kids yet. At the time, it was a huge push in the field."

In Arredondo's case, the pressure in his lungs was too high to allow for an immediate heart transplant, so the care team decided that a VAD would allow the lungs to recover and the pressure to fall so that he could undergo a heart transplant in the future.

In addition to providing medical care, a significant part of the VAD program is dedicated to educating patients and their families about the device, setting patients on a path to outpatient life.

"We train parents and siblings how to be 'VAD active'," Lin said. "We teach them how to change the batteries and when to call the hospital. We also inform the emergency medical service providers in the community where the patient lives to make them aware."

When they were in high school together, Arredondo's sister Viviana would help him change his batteries every day at lunchtime.

"We learned to make the VAD a part of our lives. Sometimes when our mom is not home at night, I help Edgar get in bed and connect him to his home monitoring system," Viviana said.

The program also addresses patients' concerns about issues such as body image, being reliant on a machine and getting treated differently. This support makes patients and their families feel confident about living life outside the hospital.

"Our hospital community is very motivated to be involved in the care of these patients. It takes a lot of manpower to get these kids back to being kids, which is one of the main goals of pediatric VAD support," said nurse practitioner Jenna Murray, RN, a ventricular assist device coordinator.

Arredondo has made a lasting impression on the hearts of his health-care team.

This is especially true for Lin, who has taken care of him from the beginning and even attended his high school graduation.

"I feel incredibly lucky to know someone like Edgar and to be a part of his care," Lin said. "It's amazing to see him endure all of these things and take it all in stride. He hasn't missed a step." **ISM**