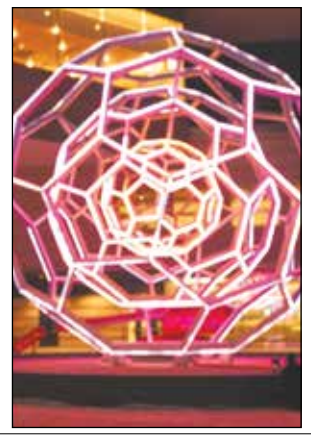
INSIDE STANFORD MEDICINE

Volume 11, No. 15 ■ August 19, 2019 ■ Published by the Office of Communication & Public Affairs



The new Stanford Hospital, includes four acres of outdoor gardens and more than 400 works of original art.

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One therapy bests others at motivating kids with autism to speak, study finds

By Erin Digitale

Pivotal response treatment involving parents works better than other existing therapies at motivating children with autism and significant speech delays to talk, according to the results of a large study by researchers at the School of Medicine.

Because children with autism are less socially motivated than typically developing children, parents' instincts about how to engage them often don't succeed, said Grace Gengoux, PhD, clinical associate professor of psychiatry and behavioral sciences. PRT gives parents a way to breach this barrier.

"We were teaching parents how to set up situations where their child would be motivated to communicate," Gengoux said. "The results of our study are exciting because we found that children in the PRT group improved not just in their communication skills, but also in their broader social abilities."

Heidi Pim of Palo Alto, California, participated in the study with her son, James, who was diagnosed as a toddler with autism and speech delays.

"I was really worried and anxious about not knowing if he would ever be able to talk," Pim said. She was impressed by the changes she saw in James, who was 3 at the time of the study. "I feel so grateful now to see how many words and phrases he knows," she said. "He's able to speak clearly and socialize as well, to go up to people and ask them questions."

"I feel so grateful now to see how many words and phrases he knows."

A paper describing the study was published online Aug. 5 in *Pediatrics*. Gengoux is the lead author. The senior author is Antonio Hardan, MD, professor of psychiatry and behavioral sciences.

The six-month study enrolled 48 children who were 2 to 5 years old and had autism and significant language delays. Half the children received PRT treatment from therapists and their parents, while the remaining children continued to receive whatever autism treatments they had been getting before the study began, which included other types of applied behavior analysis and conventional speech therapy.

Training parents

For the first 12 weeks of the study, children in the PRT group underwent 10 hours per week of PRT from a trained therapist, and their parents received training for one hour per week in how to use the treatment's techniques during everyday interactions with their children. For the second 12 weeks of the study, children in the PRT group received five hours per week of therapist treatment, and their parents had monthly instruction sessions.

In PRT, the therapist or parent notes what the child is interested in, and uses the object to encourage speech. For example, if James wanted a toy car, Pim, his mother, learned to pick up the car, hold it where he could see it and encourage him to say "car." When he tried to say the word, he was rewarded with the toy.

At first, James learned single words. He then progressed to phrases such as "green car" and "ready, set, go." Pim also used PRT to help James learn to express his needs, such as by saying "bottle" if he was thirsty.

"He used to not be able to point to something or ask," Pim said. "PRT really improved his vocabulary skills and communication back and forth. It helped us understand what he needs and wants."

COURTESY OF HEIDI PIM

Five years ago, James Pim, who has autism, and his mother participated in a Stanford study of pivotal response training.

As the trial progressed, Pim also saw James' frustration levels decrease. "Before, he didn't know how to express his feelings," she said. "When I would leave for the day and come back, he didn't See AUTISM, page 6

Forgotten immune cells protective in mouse model of multiple sclerosis

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New research shows that immune cells known as CD8 T cells helped reduce the severity of a disease similar to multiple sclerosis in mice.

By Jonathan Wosen

A seldom-studied class of immune cells may reduce the friendly fire that drives autoimmune disease, according to a new study by researchers at the School of Medicine.

Stimulating these protective cells could lead to new therapies for diseases in which the immune system attacks the body's own tissues, such as multiple sclerosis and celiac disease.

In the study, published Aug. 7 in *Nature,* researchers tracked immune cells in the blood of mice with a disease akin to multiple sclerosis. They discovered a rise in CD8 T cells, typically See CELLS, page 7

Major effort launched to harness microbiome for disease treatment

Stanford is launching a major new effort to harness the communities of microbes inhabiting our bodies — known as the microbiome — in developing new therapies for debilitating diseases.

The Stanford Microbiome Therapies Initiative (MITI), a joint initiative between Stanford ChEM-H and the Department of Bioengineering, is backed by a $10 million gift from Marc and Lynne Benioff and a $7 million gift from Mark and Debra Leslie.

The initiative has an ambitious goal of building and manipulating the microbiome to create new therapies and test them in early-stage human clinical trials.

"Microbiome science has great potential for advancing our understanding and treatment of human disease," said Stanford President Marc Tessier-Lavigne, PhD. "Stanford faculty are studying the microbes that inhabit our bodies in health and disease and developing platforms to generate new therapies. This body of work creates a foundation for the Stanford Microbiome Therapies Initiative, which will foster interdisciplinary collaborations across the university to spark discoveries that will benefit patients. I'm thankful to Marc and Lynne Benioff for seeing the potential of this promising field and making a generous gift to inspire other philanthropists, to the deans of the schools of Medicine and Engineering for their leadership in developing this new initiative, and to Mark and Debra Leslie for joining the Benioffs with their generous support."

Lloyd Minor, MD, dean of the Stanford School of Medicine, said, "The vast number of microbial cells living inside and on the human body represent an uncharted but important frontier in health care. A greater understanding of the microbiome will allow us to harness this system to not just treat disease but to cure it altogether. We look forward to collaborating with the School of Engineering to realize the potential of these microbial communities, and we are grateful to Marc and Lynne Benioff for sharing our vision, and to Mark and Debra Leslie for extending their support."

The Benioffs announced their lead gift to Stanford along with funding for the University of California-San Francisco to create the See MICROBIOME, page 7

L.A. CICERO/STANFORD NEWS SERVICE

Michael Fischbach will lead the Microbiome Therapies Initiative.

Human microbiome churns out thousands of tiny novel proteins

By Krista Conger

Your body is a wonderland. A wonderland teeming with trillions of bacteria, that is. But it's not as horrifying as it might sound. In fact, there's mounting evidence that many aspects of our health are closely intertwined with the composition and hardiness of our microscopic compatriots, though exactly how is still mostly unclear.

Now, researchers at the School of Medicine have discovered that these microbial hitchhikers — collectively known as the human microbiome — are churning out tens of thousands of proteins so small that they've gone unnoticed in previous studies. The proteins belong to more than 4,000 new biological families predicted to be involved in, among other processes, the warfare waged among different bacterial strains as they vie for primacy in coveted biological niches, the cell-to-cell communication between microbes and their unwitting hosts, and the critical day-to-day housekeeping duties that keep the bacteria happy and healthy.

Because they are so small — fewer than 50 amino acids in length — it's likely the proteins fold into unique shapes that represent previously unidentified biological building blocks. If the shapes and functions of these proteins can be recreated in the lab, they could help researchers advance scientific understanding of how the microbiome affects human health and pave the way for new drug discovery.

A paper describing the research findings was published Aug. 8 in *Cell*. Ami Bhatt, MD, PhD, assistant professor of medicine and of genetics, is the senior author. Postdoctoral scholar Hila Sberro, PhD, is the lead author.

'A clear blind spot'

"It's critically important to understand the interface between human cells and the microbiome," Bhatt said. "How do they communicate? How do strains of bacteria protect themselves from other strains? These functions are likely to be found in very small proteins, which may be more likely than larger proteins to be secreted outside the cell."

But the proteins' miniscule size had made it difficult to identify and study them using traditional methods.

"We've been more likely to make an error than to guess correctly when trying to predict which bacterial DNA sequences contain these very small genes," Bhatt said. "So until now, we've systematically ignored their existence. It's been a clear blind spot."

It might be intimidating for the uninitiated to think too deeply about the vast numbers of bacteria that live on and in each of us. They account for far more cells in and on the human body than actual human cells do. Yet these tiny passengers are rarely malicious. Instead, they help with our digestion, supplement our diet and generally keep us running at our peak. But in many cases, it's been difficult to pick apart the molecular minutiae behind this partnership.

NORBERT VON DER GROEBEN

Ami Bhatt and her colleagues found that bacteria in and on our bodies make thousands of tiny, previously unidentified proteins that could shed light on health and advance drug development.

Bhatt and her colleagues wondered if answers might be found in the small proteins they knew were likely to wiggle through the nets cast by other studies focusing on the microbiome. Small proteins, they reasoned, are more likely than their larger cousins to slip through the cell membrane to ferry messages — or threats — to neighboring host or bacterial cells. But how to identify and study these tiny Houdinis?

> "The bacterial genome is like a book with long strings of letters."

"The bacterial genome is like a book with long strings of letters, only some of which encode the information necessary to make proteins," Bhatt said. "Traditionally, we identify the presence of protein-coding genes within this book by searching for combinations of letters that indicate the 'start' and 'stop' signals that sandwich genes. This works well for larger proteins. But the smaller the protein, the more likely that this technique yields large numbers of false positives that muddy the results."

A big surprise

To tackle the problem, Sberro decided to compare potential small-protein-coding genes among many different microbes and samples. Those that were identified repeatedly in several species and samples were more likely to be true positives, she thought. When she applied the analysis to large data sets, Sberro found not the hundreds of genes she and Bhatt had expected, but tens of thousands. The proteins predicted to be encoded by the genes could be sorted into more than 4,000 related groups, or families, likely to be involved in key biological processes such as intercellular communication and warfare, as well as maintenance tasks necessary to keep the bacteria healthy.

"Honestly, we didn't know what to expect," Bhatt said. "We didn't have any intuition about this. The fact that she found thousands of new protein families definitely surprised us all."

The researchers confirmed the genes encoded true proteins by showing they are transcribed into RNA and shuttled to the ribosome for translation — key steps in the protein-making pathway in all organisms. They are now working with collaborators to learn more about the proteins' functions and to identify those that might be important to the bacteria fighting for space in our teeming intestinal carpet, for example. Such proteins might serve as new antibiotics or drugs for human use, they believe.

"Small proteins can be synthesized rapidly and could be used by the bacteria as biological switches to toggle between functional states or to trigger specific reactions in other cells," Bhatt said. "They are also easier to study and manipulate than larger proteins, which could facilitate drug development. We anticipate this to be a valuable new area of biology for study."

Other Stanford co-authors are graduate student Brayon Fremin; postdoctoral scholars Soumaya Zlitni, PhD, and Fredrik Edfors, PhD; and Michael Snyder, PhD, professor and chair of genetics.

Researchers from One Codex, the Joint Genome Institute of the Department of Energy, the Alexander Fleming Biomedical Sciences Research Center in Greece, and Lawrence Berkeley National Laboratory also contributed to the study.

The study was supported by the National Institutes of Health, the PhRMA Foundation, the U.S. Department of Energy and a Damon Runyon Clinical Investigator Award.

Stanford's departments of Medicine and of Genetics also supported the work. ISM

Researchers discover gel reduces scar tissue after surgery in animals

By Mandy Erickson

Researchers at Stanford have found that spraying a gel on the internal tissues of animals after cardiac surgery greatly reduces adhesions, fibrous bands that form between internal organs and tissues. Adhesions can cause serious, even fatal, complications.

The gel, developed at Stanford to deliver medications, was far more effective than adhesion prevention materials currently on the market, the researchers said. It appeared to be safe in the animal study.

"The difference between what we saw after using the gel and what we normally see after surgery was drastic," said Joseph Woo, MD, professor and chair of cardiothoracic surgery and the Norman E. Shumway Professor.

A paper describing the research was published Aug. 7 in *Nature Biomedical Engineering*. Woo and Eric Appel, PhD, assistant professor of materials science and engineering, are the senior authors. Lyndsay Stapleton, a graduate student in bioengineering, is the lead author.

Adhesions form after 95% of surgeries. Some are harmless, but after abdominal surgeries, they can twist or compress the intestines, causing life-threatening blockages. Gynecological surgery can also lead to adhesions that cause infertility. In cardiac re-operations, common for those born with heart defects, adhesions increase the risk of complications.

Previous methods, lot of failures

Methods to prevent adhesions — including animal membranes, sheets of rubber and mineral oil — have existed for more than 100 years, but they have mostly failed. Current adhesion barriers approved by the Food and Drug Administration are rarely used; they are difficult to deploy and are considered ineffective.

> "I thought, 'Oh wow, we could be onto something here.'"

The Stanford researchers had long pondered a solution to the adhesion problem. But one day, when Stapleton was working with lab rats to develop an injectable therapy to reduce tissue damage following a heart attack, Appel suggested she try spraying a polymer-nanoparticle hydrogel onto the hearts and surrounding tissue after surgery to see if it reduced the formation of adhesions. Weeks later, when she operated on the animals again, she saw that no adhesions had formed.

"It was pretty striking," she said. "I thought, 'Oh wow, we could be onto something here.'"

The researchers decided to conduct a study. First, they formulated four additional gels with a range of properties. Then, after inducing heart attacks in rats, they randomly divided the animals into eight treatment groups: five that each received a different gel, two that received commercially available adhesion barriers and one that received no treatment.

Four weeks later, the rats that had received no treatment or either of the two commercial adhesion barriers had formed dense adhesions: Their hearts were connected to their chest walls. The rats that were treated with two of the five gels had formed moderate to dense adhesions. The rats treated with the other three gels fared much better, with very few adhesions. PNP 1:10, the gel Stapleton initially tried, completely prevented adhesions.

Like mayonnaise

The researchers then tested PNP 1:10 in sheep, whose hearts are similar in size and shape to

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Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
455 Broadway, 4th floor
Redwood City, CA 94063
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

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STANFORD MEDICINE

Fast communication allows microbes to release toxins in unison

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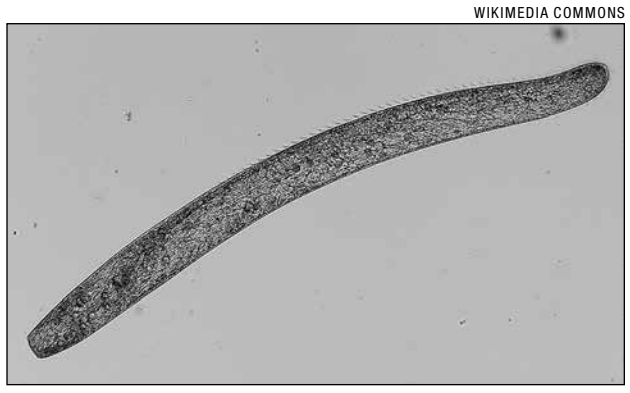


A single-celled organism called a Spirostomum. Individual Spirostomum can coordinate their ultrafast contractions so closely that groups of them appear to shrink simultaneously — a reaction to predators that makes them release paralyzing toxins in sync.

By Taylor Kubota

Crouching in the boot-sucking mud of the Baylands Nature Preserve in Palo Alto, California, Manu Prakash, PhD, associate professor of bioengineering at Stanford, peered through his Foldscope — a $1.75 origami microscope of his own invention — scrutinizing the inhabitants of the marsh's brackish waters. With his eye trained on a large single-cell organism, called Spirostomum, he watched it do something that immediately made it his next research subject.

"I still remember for the very first time seeing this organism swim by under the Foldscope," Prakash said. "This is a massive cell, but it contracts in less than a blink of an eye, accelerating faster than almost any other single cell. When you aren't expecting it, it's like it disappears. I remember being so excited, I had to bring the cells back to the lab and take a careful look."

This observation, made through a simple tool only 5 miles from Prakash's lab, has now led him and colleagues to the discovery of a new form of communication between cells, which they detail in a paper published July 10 in *Nature*. Without touching and without electrical or chemical signals, individual Spirostomum can coordinate their ultrafast contractions so closely that groups of them appear to shrink simultaneously — a reaction to predators that makes them release paralyzing toxins in sync.

> "This is a massive cell, but it contracts in less than a blink of an eye."

"There are many different ways of communication in biology, but this is really a new kind of signaling between cells that we're trying to understand," said Arnold Mathijssen, PhD, a postdoctoral scholar in the Prakash lab and lead author of the paper. "It's possible this is more universal than we've described so far and is a way many different kinds of organisms communicate."

From benches to black holes

The Prakash lab gathers wild samples of various tiny organisms from an area they call Peggy's Bench, so named for a nearby memorial bench, and they've been coming here for years, often a couple times a week. Mixed salt and fresh waters, changing tides and bird migrations make the marsh a potential biodiversity hot spot. Although Prakash knew none of that when he first visited.

"Lake Lagunita had dried out and I was looking for a new place to sample," recalled Prakash, referring to a small seasonal lake on the Stanford campus. "I looked in the GPS map on my phone, and I saw this blue spot. I didn't know anything about it in the beginning, but it was worth a try."

Back in the lab, the group studied wild samples of Spirostomum while also growing their own cultures of Spirostomum ambiguum, and began a deep dive into details of this ultra-fast contraction. Using high-speed imaging, they found it happens in 5 milliseconds — the human eye takes 100-400 milliseconds to blink — and that the cell endures about 14 times the force of gravity in the process. As it shrinks, pouches of toxin break off from the cell's edges and release their contents into the surrounding fluid.

During one late night in the lab, the researchers also noticed that, when in clumps, the cells seemed to all contract at the same time.

"We wondered, 'How can cells that are almost centimeters away from each other synchronize to do something almost simultaneously?'" said co-author Saad Bhamla, PhD, a former postdoctoral scholar in the Prakash lab who is now an assistant professor at the Georgia Institute for Technology.

The researchers solved this mystery by applying insights from separate research being conducted by Deepak Krishnamurthy, a graduate student in the Prakash lab, on how an individual cell can sense the movement of water around it. Once they observed the flow fields around Spirostomum, it became clear that they were communicating via hydrodynamic flows.

KURT HICKMAN

Observations of cellular life from the Baylands Nature Preserve in Palo Alto, California, led Manu Prakash and his fellow researchers to the discovery of a new type of intercellular communication.

"The first cell contracts and generates a flow, which triggers the second, and that one triggers the third. So, you get this propagating trigger wave that passes through the whole colony," Mathijssen said. "These are big, long-range vortex flows, and the velocities of the communication rise up to meters per second — even though each cell is only 1 to 4 millimeters long."

Mathijssen figured out what triggers the first cell to contract through an experiment that Prakash and Krishnamurthy had already built for Krishnamurthy's research. By sucking liquid ever so carefully out of a small hole in a pair of slides containing S. ambiguum, Mathijssen mimicked the eating action of its predators. The closer to the hole the cell moved, the more one end of its body was stretched relative to the other — as happens when an object approaches a black hole. With this simple and relatively large-scale experiment, researchers determined that a specific amount of bodily tension likely causes the opening or closing of tension gated ion channels within S. ambiguum, making it contract.

Where the wild things are

The Prakash lab and Bhamla lab continue to work on S. ambiguum to learn more about how, when and why these cells contract. They also want to know whether the hydrodynamic communication they've discovered is used by other organisms, because in nature both generating and sensing flows is essential for survival. As part of this research and other work, the Prakash lab has been regularly returning to Peggy's Bench.

"Even though this spot was an accidental discovery for me, we're working on several projects in the lab that have been inspired by what we've collected right here," said Prakash, while standing at the edge of the marsh. "This work is just one example of many hidden gems we can find when we step outside the lab — and literally anyone with simple frugal tools, like Foldscope, can uncover and start exploring."

In the near future, Prakash is planning an extensive biodiversity survey in the marsh where they collect Spirostomum, which would include setting up a microscope-based live feed video of their subjects' watery world and bringing undergraduate students to explore this swampy field.

Prakash is a member of Stanford Bio-X and the Stanford Maternal & Child Health Research Institute; a fellow of Stanford ChEM-H; and an affiliate of the Stanford Woods Institute for the Environment.

Another researcher from Georgia Tech also contributed to the research, which was funded by the Human Frontier Science Program, the National Science Foundation Center for Cellular Construction, the U.S. Army Research Laboratory and the U.S. Army Research Office, the Chan Zuckerberg Biohub and the Howard Hughes Medical Institute.

Stanford's Department of Bioengineering, which is jointly managed by the School of Medicine and School of Engineering, also supported the research. ISM

Adhesions

continued from page 2

human hearts; they found similar results.

PNP 1:10 was stiff enough to stick, but not so stiff it detached from the organs, Appel said. "It was sort of a Goldilocks sweet spot." He compared PNP 1:10 to mayonnaise: thick, but easily spreadable. That property allows it to be sprayed onto an organ but then immediately reform its original strength.

Joseph Woo

The gel also has the ideal tension between stickiness and slipperiness: "It covers all of the irregular surfaces of the heart, adhering to the tissues, but not to itself," said Woo, who treats heart patients at Stanford Health Care.

And it's flexible, allowing the heart to beat: "The gel doesn't prevent tissues from moving around," Appel said. "It simply provides a physical barrier to keep them from sticking to each other."

PNP 1:10 dissolves and is absorbed by the body about two weeks after its application — enough time for healing to occur, Appel said. PNP 1:10 is not approved for use in patients, but it is made of components that the Food and Drug Administration has approved. As part of the study, the researchers tested the rats to see if they showed any reaction to the gel; they saw no abnormalities in the surrounding tissues or in the blood.

The researchers next plan to try PNP 1:10 in abdominal surgery in rats. They hope to conduct human trials soon.

Woo and Appel are members of Stanford Bio-X. Woo is associate director of the Stanford Cardiovascular Institute, and Appel is a faculty fellow at Stanford ChEM-H.

Eric Appel

Other Stanford study coauthors are graduate students Amanda Steele, Anthony Yu and Gillie Agmon; cardiothoracic surgery residents Hanjay Wang, MD, and Michael Paulsen, MD; postdoctoral scholars Hector Lopez Hernandez, PhD, and Yuko Tada, PhD; visiting scholar Anton Smith, PhD; research assistants Akshara Thakore, Haley Lucian, Anahita Eskandari, Justin Farry and Kevin Jaatinen; undergraduate student Kailey Totherow; clinical veterinarian Sam Baker, DVM; former research assistant Camille Hironaka; medical student Kiah Williams; perfusionists Hunter Bergamasco, Clifton Marschel and Blaine Chadwick; and Michael Ma, MD, assistant professor of cardiothoracic surgery.

The work was funded by Stanford Bio-X, the Stanford-Coulter Translational Research Grants Program, the National Institutes of Health, the American Heart Association, the National Science Foundation-funded California Alliance, a Stanford Interdisciplinary Graduate Fellowship and the American Association for Thoracic Surgery.

Stanford's departments of Cardiothoracic Surgery and of Materials Science and Engineering also supported the work. ISM

Cigarettes with eco-friendly marketing seen as less harmful

By Rob Jordan

Few people would consider a handgun with a sustainably harvested wood stock any less lethal than one with a steel stock. The same logic doesn't seem to apply to cigarettes, the leading preventable cause of death globally and in the United States. A new Stanford study finds that people perceive cigarettes with pro-environment marketing on the packaging as less harmful not only to the environment but also to the health of smokers and people around them.

The survey, published online July 17 in *Preventive Medicine*, is the first to gauge the effect of such marketing on cigarette packaging, which is viewed about 20 times a day by the average pack-a-day smoker.

"Eco-friendly and natural food products are seen as safer for health," said study lead author Anna Epperson, PhD, a postdoctoral scholar with the Stanford Prevention Research Center. "That couldn't be further from the truth when it comes to cigarettes."

On average, smokers die 10 years earlier than nonsmokers, according to the Centers for Disease Control and Prevention. While they're alive, they're at significantly higher risk for cancer, heart disease, stroke, lung diseases, diabetes and a raft of other maladies.

Every year in the United States, cigarette smoking is responsible for more than 480,000 deaths (a number greater than the population of Oakland, California), including more than 41,000 deaths resulting from secondhand smoke exposure. And cigarettes aren't just a health scourge. They are also the most commonly discarded form of litter in the world, defiling just about every kind of natural landscape and built environment with toxic chemicals that leach into soil and water supplies.

JUDITH PROCHASKA

The Natural American Spirit brand of cigarettes markets itself as pro-environment on its packaging.

Responsible cigarettes?

The researchers compared two major cigarette brands: Pall Mall, marketed as a discount brand, and Natural American Spirit, a super-premium brand that features a pro-environment marketing campaign — the first-ever corporate social responsibility advertising on cigarette packaging. That campaign includes a description of a manufacturing facility that is "zero-waste-to-landfill" and features a wreath of three tobacco leaves that mimics the symbol for recycling, as well as the logo for the Programme for the Endorsement of Forest Certification, an international organization that promotes sustainable forest management.

Both brands have the same health impacts and are owned by the same company, Reynolds American. Still, survey participants — including former smokers, current smokers and people who had never smoked — consistently ranked Natural American Spirit as less harmful to health and the environment. The findings were strongest among current smokers, a factor that could discourage quitting and might encourage switching to the brand, according to the researchers. Whereas never and former smokers likely have developed a firmer stance than current smokers on the harms of smoking, many current smokers may be seeking a product alternative that reduces smoking harms to both humans and the planet, the researchers explained.

Every year, cigarette smoking is responsible for more than 480,000 deaths nationwide.

In 2006, a federal court concluded that the tobacco industry had deceived the American public for more than 50 years about the harms of smoking and secondhand smoke. The court suggested the word "natural" be banned from cigarette marketing and brand names. "Our findings reinforce the court's conclusion that positioning cigarettes as 'natural' deceives the American public of the harms of smoking," said Judith Prochaska, PhD, MPH, associate professor of medicine.

Aggregating pro-environment and health-related claims is nothing new in marketing. While it may be justified for organic agriculture products, for example, it is not a generally valid principle, according to study co-author Eric Lambin, PhD, professor of Earth system science and the George and Setsuko Ishiyama Provostial Professor. "People need to be made aware of the risk of being manipulated by big brands that appeal to the environmental values of consumers to sell them products that are bad for their health."

Sustaining addiction

In an earlier, related study, the researchers found that the Natural American Spirit pack design, which also features icons of an American Indian smoking a pipe and a mythological thunderbird, creates misperceptions that the brand is American Indian-owned or grown on tribal land and, in turn, healthier and more desirable.

The researchers suggest regulations to prohibit using the word "natural" in tobacco brand names or using pro-environment language and imagery on cigarette packs. Instead, they propose mandating plain packaging for cigarettes.

"All commercially available cigarettes in the U.S. are designed to create and sustain addiction and will kill half of all long-term users if smoked as intended," the researchers write. "Marketing language that obscures these health harms, even indirectly through questionable pro-environment claims, ought to be prohibited."

Lambin is also a senior fellow at the Stanford Woods Institute for the Environment; an affiliate of Stanford's Center on Food Security and the Environment; and a professor at the Catholic University of Louvain in Belgium.

Other Stanford co-authors are senior research scholars Lisa Henriksen, PhD, and June Flora, PhD; and Mike Baiocchi, PhD, assistant professor of medicine.

Prochaska has provided consultation to pharmaceutical and technology companies that make medications and other treatments for quitting smoking and has served as an expert witness in lawsuits against the tobacco companies. The research was funded by the Stanford Woods Institute for the Environment's Environmental Venture Projects program. **ISM**

Researchers are building glove to treat symptoms of stroke

By Nathan Collins

The most obvious sign someone has survived a stroke is usually some trouble speaking or walking. But another challenge may have an even greater impact on someone's daily life: Often, stroke survivors lose sensation and muscle control in one arm and hand, making it difficult to dress and feed themselves or handle everyday objects such as a toothbrush or door handle.

Now, researchers at Stanford are working on a novel therapy that could help more stroke survivors regain the ability to control their arms and hands — a vibrating glove that gently stimulates the wearer's hand for several hours a day.

Caitlyn Seim, PhD, a postdoctoral scholar at Stanford, began the project as a graduate student in human-centered computing at Georgia Tech in the hope that the glove's stimulation could have some of the same impact as more traditional exercise programs. After developing a prototype, she approached Stanford colleagues Maarten Lansberg, MD, PhD, an associate professor of neurology, and Allison Okamura, PhD, a professor of mechanical engineering, in order to expand her efforts. With help from a Neuroscience:Translate grant from the Wu Tsai Neurosciences Institute at Stanford, the trio are working to improve on their prototype glove and bring the device closer to clinical testing.

"The concept behind it is that users wear the glove for a few hours each day during normal daily life — going to the supermarket or reading a book at home," Seim said. "We are hoping that we can discover something that really helps stroke survivors."

COURTESY OF CAITLYN SEIM

A glove being developed by Stanford researchers aims to treat symptoms of stroke through vibration.

Reaching for new stroke therapies

Seim, Lansberg and Okamura's goal is a tall order. Despite some individual success stories, the reality is that most stroke patients struggle to regain the ability to speak, move around and take good care of themselves.

"Stroke can affect patients in many ways, including causing problems with arm function, gait, vision, speech and cognition," Lansberg said. Yet despite decades of research, "there are essentially no treatments that have been proven to help stroke patients recover these functions," he added.

It was in that context that the three researchers independently started thinking about what they could do to improve the lives of people who have survived strokes. As the medical doctor in the bunch, Lansberg had already been treating stroke patients for years and has helped lead the Stanford Stroke Collaborative Action Network, or SCAN, another project of the Wu Tsai Neurosciences Institute. Okamura, meanwhile, has focused much of her research on haptic, or touch-based, de-

vices, and in the last few years her lab has spent more and more time thinking about how to use those devices to help stroke survivors.

"Rehabilitation engineering provides a unique opportunity for me to work directly with the patients who are affected by our research," Okamura said. "The potential to translate the kind of technology relatively quickly to a commercial product that can reach a large number of stroke patients in need of therapy is also very exciting."

For her part, Seim's interest in stroke stems from an interest in wearable computing devices. Yet rather than build more virtual-reality goggles and smartwatches, Seim said she wants to apply wearable computing to the areas of health and accessibility — "areas which have some of the most compelling problems to me."

Growing a new idea

With that ambition in mind, Seim built a vibrating glove prototype that she hoped would stimulate nerves and improve both sensation and function in stroke survivors' hands and arms. After collecting some promising initial data, Seim reached out to the Stanford team.

"Stanford has SCAN and StroKeNet, along with a community of interdisciplinary engineering and computing research, so I reached out to Maarten, and he was very supportive," Seim said.

Now, Seim, Lansberg and Okamura are revising the glove's design to improve its function and to add elements for comfort and accessibility. Then, they'll begin a new round of clinical tests at Stanford.

Long term, the hope is to build something that helps stroke survivors recover some of the functions they have lost in their hands and arms. And if initial tests work out, Lansberg said, it's possible the same basic idea could be applied to treat other complications associated with stroke.

"The glove is an innovative idea that has shown some promise in pilot studies," Lansberg said. "If proven beneficial for patients with impaired arm function, it is conceivable that variations of this type of therapy could be developed to treat, for example, patients with impaired gait."

Lansberg and Okamura are members of Stanford Bio-X and the Wu Tsai Neurosciences Institute. **ISM**

At new adult hospital, art and nature aim to benefit healing

By Grace Hammerstrom

In the early 1980s, a group of volunteers formed to acquire and hang art on the then-empty walls of Stanford Hospital. What this group sensed about the power of art — that it could help improve healing — was proven later that same decade in multiple studies by environmental psychologist Roger Ulrich, PhD, and others. Their research findings indicated that art can substantially affect outcomes such as blood pressure, anxiety, intake of pain medications and length of hospital stay. Similarly, Ulrich found that patients who had hospital rooms with a window required less pain medication and recovered faster than patients in rooms without windows.

"Today, every new hospital includes art," said Connie Wolf, consulting director of the art program for the new Stanford Hospital. "Integrating art into the hospital environment allows us to think holistically about the healing of the mind, the soul and the spirit."

The new Stanford Hospital, which will open in the fall, places equal value on the restorative qualities of art and nature. It includes four acres of outdoor gardens, floor-to-ceiling windows in every patient room and more than 400 works of original art.

"We think about patients, their loved ones and families and the staff. Those three groups of people are all important to nurture," Wolf said. "How can we create an environment that supports the patients' healing and well-being, provides comfort to their families and offers relief to the complex and challenging work of the staff?"

Stanford Health Care has a dedicated art commission, comprised of 14 volunteers led by Linda Meier, who also serves on the Stanford Health Care board of directors. The commission reviews all the work for the new hospital and strives to find pieces that are not only uplifting, beautiful and inspiring, but also have depth, complexity and layers of meaning. Patients and families can spend long periods of time at the hospital, she said. "We want them to be able to come back to the work and experience something different every time."

STEVE FISCH

Leo Villareal stands near his sculpture Buckyball, which was installed at the entrance to the new hospital.

The committee commissioned seven pieces of art for the new Stanford Hospital, all of which have been generously supported by donors. These site-specific works grace the entrance plaza, the atrium, the walls of the interfaith chapel and the third floor galleria and gardens. Along with the hospital's gardens, the art will help create a mood, Wolf said. "We want people to walk in, feel welcome, and know they are in a place where their health and spirit matter."

CONNIE WOLF

Artist Jinnie Seo (right) and studio assistant Jihyun Lee during the production of "Rays of Hope," a mural in the chapel of the new hospital.

'Rays of Hope'

Korean artist Jinnie Seo spent two months on-site at the new hospital painting "Rays of Hope," a mural in the interfaith chapel. She used a rendering as a guideline, but every stroke was free-form and spontaneous as she drew inspiration from the space. Working six days a week, Seo and her assistant brought the curved walls at the back of the chapel to life with 14 layers of cerulean blue. Next, Seo applied a series of fine, straight lines that create the impression of curves and movement. For some, the image is reminiscent of butterflies taking flight, she said. Using 12 different shades of metallic paint with a high-gloss varnish finish, the mural shimmers in the chapel's natural light.

"I'm inspired by light. There's physical light and spiritual light and light within each of us," Seo said. "I wanted to give a person a space to pause and be still, even for one moment. That moment can last an eternity and be a life-changing experience."

Buckyball

Leo Villareal brought his passion for form and geometry to his larger-than-life sculpture Buckyball, a 30-foot metal structure featuring three nested spheres. The centerpiece of the new hospital's entrance plaza, Buckyball will be illuminated by LED lights at night in a never-repeating sequence of colors and patterns. Villareal was inspired by the geodesic dome popularized by architect and inventor Buckminster Fuller.

"I've always been interested in underlying structures and rules and geometry," Villareal said. This same geodesic structure was discovered in a carbon molecule by nanotechnologists, he added. "I thought it would be interesting to take something that you could never see with a naked eye and expand it on this monumental scale."

Villareal is best known locally for transforming the Bay Bridge and the San Francisco skyline with his Bay Lights installation. As he did with the Bay Bridge, he has lined Buckyball with LED light strips, and programmed them to twinkle, blink and slowly shift to create a mesmerizing pattern of light each evening.

Other commissioned works in the new hospital include two commissioned artworks in the atrium. Zadok Ben-David's Endless Columns present images of butterflies and the human figure that soar in the space. In creating Liquid Light, artist James Carpenter used large waves of tumbled glass woven together to create a "reflecting pond" directly under the glass dome in the hospital's atrium. Reflecting light throughout the day, the sculpture provides different experiences when you walk around it or look down on it from the upper levels.

Ned Kahn's Air Cube, a 1,000-pound metal sculpture that interacts with the wind, is installed in the garden space on the third floor. Kahn's work aims to symbolically replicate the forms and forces of nature; he strives to create art that interacts with natural processes. Air Cube is lined with rows of metal flaps that move freely and reflect light in dynamic and ever-changing ways.

The third floor will also be distinguished by a wall mural based on a drawing by the late artist Sol LeWitt. He is best known for his bold, colorful, geometric works comprised of straight lines and curves. In July, two master painters experienced in making these works, together with two Stanford undergraduate students serving as interns, spent 24 days painting the LeWitt mural. The process entailed using nearly 75 rolls of masking tape to delineate each line. Like all of LeWitt's works, the original drawing was adjusted to be specific to the space and fills every inch of the 18-by-10-foot wall on the third floor.

Each of the seven commissioned pieces for the new Stanford Hospital were fully underwritten by private donors. The other 400-plus pieces of art were either donated works or acquired with private monetary donations.

Healing gardens

Today, both art and gardens have become standard elements in hospitals adhering to the practices of evidence-based design, which uses credible research to inform decisions about the environment to achieve the best possible outcomes for patients. Four acres of gardens surround the new Stanford Hospital, including five interconnected rooftop gardens on the third level of the building, with walking paths and multiple places to sit and take in the views of the nearby hills. A vertical garden outside the interfaith chapel on the third floor creates an additional private space for reflection.

Outside the emergency department on the first floor lies a newly planted orchard of 85 deciduous trees. Grounds crews planted six varietals of fruit, nut or flowering trees — gingko, loquat, apricot, olive, buckeye and live oak — each of which was selected for its medicinal or food-bearing properties in eastern, western and native cultures. The orchard also includes shrubs, rushes, grasses, ash trees and paths to create a shady, serene retreat for patients, families, visitors and staff. The gardens on the street-level also include a dog park, complete with a water fountain and fire hydrant.

While art will be available in the corridors connecting the patient rooms, the rooms themselves have a different kind of art on view: By design, every patient room has floor-to-ceiling windows to let in natural light while providing views of the surrounding foothills. **ISM**

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Dennis Wall on new findings in autism genetics

Autism is not one disease but several, a family of developmental disorders with similar symptoms. A rare, new subtype of autism was recently discovered by Dennis Wall, PhD, associate professor of pediatrics and of biomedical data science at the School of Medicine. Wall led research to analyze a large set of genetic data: complete genome sequences for 2,308 people from 493 nuclear families affected by autism.

Wall spoke with writer Erin Digitale about the findings, including the discovery of the rare syndrome and the identification of 16 genes that contribute to more-common forms of autism. Researchers from Stanford, UCLA, the California Institute of Technology and the Karolinska Institute contributed to the study, which was published Aug. 8 in Cell.

1 Prior research showed that autism is more than 80% genetic and may be as much as 60% heritable, meaning a large source of the disorder lies in the genetic code and may be passed from parent to child. How did we come to know that, and what does your new analysis add?

WALL: Heritability and genetic estimates come from pedigrees showing how often autism crops up in specific families, as well as from comparisons of autism rates in identical versus fraternal twins. There have been several compelling studies, including large cohort studies in Sweden and fantastic work by Stanford's Joachim Hallmayer to establish the estimates.

Dennis Wall

But the specifics of how autism is inherited haven't been well-characterized, such as which genes are important, where they're located, what variation within those genes matters or how that's transmitted from parents to offspring. Ours is the largest-ever study of multiplex families, with at least two children per family affected by autism plus an unaffected sibling. This unique dataset allows us to look at the contributions from mom and dad to all of their kids, and because we have both unaffected and multiple affected siblings, we can characterize statistically what specific inherited variants associate strongly with autism.

We need huge data sets for this work because most cases of autism come from combinations of changes in several genes. The effect size of any single gene usually explains only a tiny percentage of autism symptoms, and people without autism often have a lot of the same genetic variants as those with the disorder.

Also, although inherited risk is a big contributor to the genes we highlight, the total picture of autism vulnerability comes from the combination of inherited risk plus new genetic changes that occur spontaneously in the child. Inherited and new variants combine to create the tipping point that manifests in autism.

2 You identified 16 new autism risk genes. What's the significance of this finding?

WALL: We replicated others' findings about which genes are important to autism risk and added some new ones. Replicating previous discoveries makes those 16 new genes more believable.

What is interesting about them is that they form a network, associating with each other more tightly than you'd expect by chance. The genes are talking to each other, and this implies that there is a cascade of genetic variation that lies at the root of at least some forms of autism.

Finding and understanding this network of genes helps us clarify why a common genetic change might contribute to autism in one person but not another — in a child from our data set but not his mom or brother, for example.

We want to continue studying how different genetic changes link up with specific characteristics of people in our database, who have been very well-characterized. The network of 16 autism-risk genes is involved in chromatin remodeling during the growth of new neurons, so these genes are important to brain development, but we don't yet know exactly how they lead to autism.

3 Your work uncovered a new subtype of autism linked to mutations in a gene called NR3C2. Why is it valuable to pinpoint such a syndrome?

WALL: Although most cases of autism come from small changes in several genes, there are already a few known genetic syndromes that arise from single-gene mutations and cause autismlike behaviors, such as Rhett's syndrome, Fragile X syndrome and tuberous sclerosis.

We found three families in our study that had a previously unrecognized, rare subtype of autism associated with mutations in just one gene, NR3C2. The similarities between affected individuals from these three unrelated families are really striking. They all have an abnormal shortening of the fourth and fifth fingers of both hands; a high, arched palate; sensory hypersensitivity; and abnormal speech rhythms and patterns.

> "People without autism often have a lot of the same genetic variants as those with the disorder."

Identifying this rare syndrome is useful because it helps us parcel out our data. As we identify these rare, single-event mutations with larger genetic effects, we can essentially pull them from the "harder" group of cases, and then we should have an easier time figuring out which combinations of common genetic variants contribute to more common manifestations of autism.

And this discovery is clinically actionable. The NR3C2 mutation can be listed in genetic databases and included in genetic counseling evaluations — assuming it is replicated, of course.

4 You also created a zebrafish model of the NR3C2 mutation. What did you learn from that?

WALL: We performed a knockout experiment in this gene and saw changes in zebrafish that are consistent with what we see in humans, including social deficits and sleep disturbances. In terms of social behavior, zebrafish usually show a preference for members of their own species, but the fish with the NR3C2 mutation don't. The aberrations we saw are definitely not common in zebrafish; they don't exhibit these behaviors unless there is something wrong with their brains. We were elated to see behaviors in the fish that are consistent with what we observed in humans, and this is worthy of further study for sure.

5 Working with such a large genetic data set presents logistical challenges. How did you handle those?

WALL: These data files, consisting of whole-genome sequences for thousands of people, are big and expensive to store. It can take weeks to move them from one provider to another, and sharing data by normal means — if a scientist elsewhere says, "Hey, can you send me some data?" — can't be done. The only way to share these data is on the cloud, but storing so much data could cost as much as $20,000 per month.

Stanford reached an agreement with Amazon Web Services, which is providing free hosting of these data for the next few years, so we're in the lucky situation of being able to share data with the research community for free at www.iHART.org.

That is really important because without data sharing, replication of findings is not possible. And we're not the only experts who could find important things in these data. We have to make these data available so that everyone in the field has the opportunity to learn from them. ISM

Autism

continued from page 1

know how to say 'Mommy, I missed you,' so instead he would hit me or cry. That has lessened."

Today, James, now 8, is a happy kid who attends school in a mainstream classroom and enjoys playing with his twin sister, Jessica. Pim still uses PRT techniques to engage James in conversation on his favorite topics, such as elevators.

Speaking more

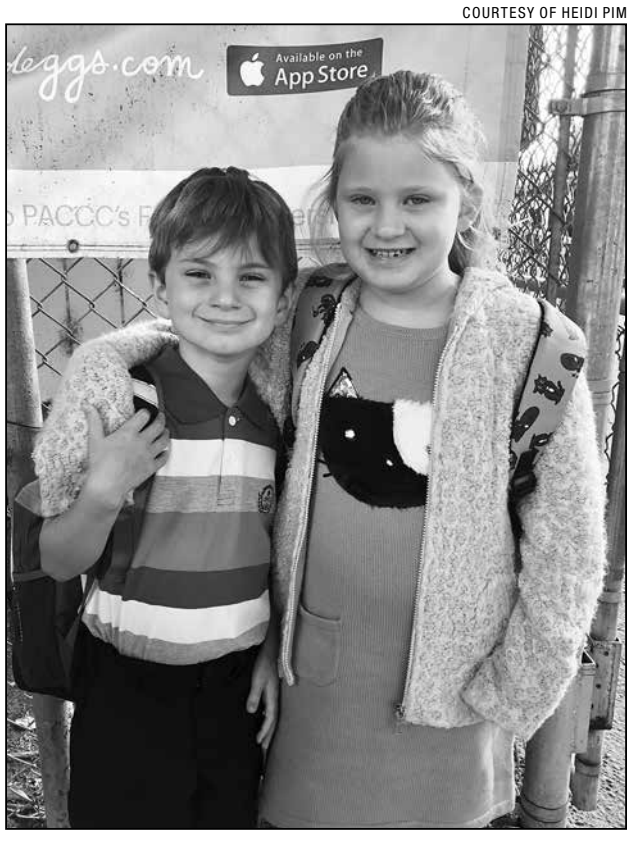
At the end of the study, the children in the PRT group spoke more than those in the comparison group, and were using common words that could be recognized by others, an important marker of progress given that many children spoke unintelligibly at the start of the trial. The children in the PRT group also showed greater improvement in a measure of their overall social communication, which is critical for an optimal long-term outcome, the researchers reported.

They also found that children who began with lower developmental abilities benefited more from the intervention, a surprising finding since many autism therapies are of greater benefit to higher-functioning children.

"It's discouraging for parents of lower-functioning kids if we tell them that higher-functioning kids do better, because higher-functioning kids are already doing better," Gengoux said. The new findings suggest that parents can play an especially valuable role in assisting children who have the greatest needs, she said, adding, "This provides a lot of hope."

Stanford researchers believe that findings from this trial are promising but that they need to be replicated in larger investigations. They are also currently recruiting young children with autism for a new study of how the brain changes in PRT. Interested parents can call (650) 736-1235 or e-mail autismdd@stanford.edu for more information.

COURTESY OF HEIDI PIM



James and his sister, Jessica. Their mother, Heidi Pim, still uses pivotal response training methods to engage James in conversation.

Parents and teachers who want to learn PRT techniques can attend a one-day conference being held at Stanford in September. More information about the conference is available at http://med.stanford.edu/autismcenter.html.

The study's other Stanford co-authors are Daniel Abrams, PhD, clinical assistant professor of psychiatry and behavioral sciences; research coordinators Rachel Schuck and Maria Estefania Millan; clinical research manager Robin Libove; clinical research coordinator Christina Ardel; and Jennifer Phillips, PhD, clinical associate professor of psychiatry and behavioral sciences.

Researchers from Palo Alto University and Autism Speaks, an autism advocacy organization, also contributed to the research.

Gengoux and Hardan are members of the Stanford Maternal & Child Health Research Institute. Hardan is also a member of Stanford Bio-X and the Wu Tsai Neurosciences Institute at Stanford.

The research was supported by grants from the National Institute on Deafness and other Communication Disorders, the National Institute of Mental Health, and the National Center for Research Resources and the National Center for Advancing Translational Sciences.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. ISM

Microbiome

continued from page 1

UCSF Benioff Center for Microbiome Medicine, which aims to radically rethink the role of the microbiome in early life and develop new interventions to prevent childhood diseases. These gifts further energize the Bay Area's thriving microbiome research community and leverage the collaborative research in this realm already taking place at the Chan Zuckerberg Biohub, a research institute affiliated with Stanford, UCSF and UC-Berkeley.

"Lynne and I are honored to support the cutting-edge research of two of the world's leading universities as they pioneer a new era of microbiome research, science and therapies," Marc Benioff said. "With a deeper understanding of the human microbiome, our generation can unlock new treatments that impact lives around the world."

Collaborative team

MITI is led by Michael Fischbach, PhD, associate professor of bioengineering. MITI leverages Stanford's extensive expertise in microbiome research, the strengths and proximity of Stanford's schools of Medicine and Engineering, and the interdisciplinary endeavors of Stanford ChEM-H (**Ch**emistry, **E**ngineering and **M**edicine for **H**uman Health).

Fischbach, who is also the Stanford MAC3 Paul and Mildred Berg Faculty Scholar and the Willard R. and Inez Kerr Bell Faculty Scholar in the School of Engineering, was recruited to Stanford in 2017 through a collaboration between Stanford ChEM-H and the Department of Bioengineering. He brought together a small group of Stanford faculty who were already working to better understand the microbiome. Fischbach proposed forming MITI (pronounced "mighty") to focus that group's efforts on manipulating microbial communities — both their composition and their genetics — and engineering those communities into therapies to address a range of diseases.

"This initiative is a perfect reflection of the ChEM-H vision of bringing together chemistry, engineering and medicine to revolutionize therapeutic development and to improve human health," said Carolyn Bertozzi, PhD, professor of chemistry and the Baker Family Co-Director of Stanford ChEM-H. "Since its inception, ChEM-H has had a strong interest in microbiome science and medicine, and we were thrilled to succeed, in partnership with the Department of Bioengineering, in recruiting Michael Fischbach to ChEM-H to lead a targeted, pioneering initiative in this area." Bertozzi is also the Anne T. and Robert M. Bass Professor in the School of Humanities and Sciences.

> An initiative focused on developing and testing new disease therapies.

The initiative draws on a culture at Stanford of working across disciplines to tackle major issues with imaginative solutions, said Kathryn Moler, PhD, vice provost and dean of research and the Sapp Family University Fellow in Undergraduate Education. "This initiative couldn't happen without the involvement and support of the deans of the schools of Medicine and Engineering and a willingness of faculty across campus to step outside their traditional domains and creatively work together to accelerate actionable discoveries and make a tangible impact in human health," she said. "The team has an ambitious goal, and I'm thankful ChEM-H is able to provide a natural home for this initiative to flourish."

Initial funding

The lead gift from Marc and Lynne Benioff, and the funds provided by Mark and Debra Leslie, will enable the Stanford MITI team to initiate the work needed to construct, manipulate and characterize novel microbial therapies for a range of human diseases. Stanford will seek additional philanthropic support in order to bring promising new therapies to early-stage human clinical trials.

Marc Benioff is the chairman, co-chief executive officer and founder of Salesforce. Lynne Benioff serves on the boards of the UCSF Foundation, UCSF Benioff Children's Hospitals and several other organizations.

Mark Leslie is founder and managing general partner at Leslie Ventures, a private investment company, and a lecturer in management at the Stanford Graduate School of Business. Debra Leslie is a director of the Leslie Family Foundation, whose mission is to positively impact lives through economic development, health care and education, and to support Jewish community life.

Focus on therapies

Much of the microbiome research currently underway focuses on sequencing and cataloging communities of microbes in our gut and on our skin — work that has led to discoveries about the role of the microbiome in diseases like inflammatory bowel disease, liver disease, autoimmune disease and cancer.

Fischbach said little has been done until now to precisely manipulate those communities or their genomes to explore possibilities for new treatments. Instead, current therapy utilizes human stool, which contains an undefined community of microbes with unknown modes of action and variable therapeutic outcomes.

"This groundbreaking research at the intersection of engineering and medicine is precisely what we envisioned when we joined forces with Stanford ChEM-H to recruit Michael Fischbach," said Jennifer Cochran, PhD, who is the Shriram Chair of the Department of Bioengineering. "Achieving this ambitious goal will draw on Stanford's expertise in engineering novel solutions and experience translating research into new therapies to be tested in humans. I appreciate the support of the schools of Medicine and Engineering and Stanford ChEM-H for their valuable teamwork in forming this new initiative."

The initiative will launch with six faculty from across engineering and medicine, plus executive and advisory committees to provide expert guidance, and is based in part on pioneering work from Alice Cheng, MD, a clinical instructor in gastroenterology at Stanford Medicine. **ISM**

Cells

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known for killing infected or cancerous cells. To their surprise, injecting mice with peptides recognized by these CD8 T cells reduced disease severity and killed disease-causing immune cells.

While the bulk of the study was done in mice, the researchers also showed that one of their central findings — an increase in CD8 T cells derived from single cells — held true in cells from people with multiple sclerosis.

The findings suggest that inflammatory and suppressive immune cells balance each other like children on a seesaw. Selectively activating suppressive CD8 T cells during autoimmune disease may help restore that balance, said Mark Davis, PhD, professor of microbiology and immunology and the study's senior author.

"We absolutely think that something like this is happening in human autoimmune diseases. It represents a mechanism that nobody's really appreciated. There's this whole subset of CD8 T cells that has a suppressive function," said Davis, who holds the Burt and Marion Avery Family Professorship and is also a Howard Hughes Medical Institute investigator. "If we could mobilize those cells to function more effectively in patients with autoimmunity, then we'd have a novel treatment for diseases like multiple sclerosis."

Attack of the T cell clones

In most cases, researchers don't know what molecules trigger autoimmune diseases, which affect 23.5 million Americans, according to the National Institutes of Health.

Multiple sclerosis is no exception. But scientists can trigger a similar disease in mice by injecting them with a small chunk, or peptide, of a protein called myelin oligodendrocyte glycoprotein, or MOG. Mice with the disease, known as experimental autoimmune encephalomyelitis, develop paralysis just like patients with multiple sclerosis.

The researchers used this mouse model of the disease to investigate what different immune cells were doing during autoimmunity. They tracked the abundance of various classes of immune cells in mice injected with MOG.

They found that the number of T cells, which act like generals in directing the overall scale and strategy behind an immune response, rose and fell like waves. DNA sequencing showed that those waves were each made of groups of identical cells — an important clue.

"When T cells encounter a pathogen, single cells that recognize some part of the pathogen divide and produce many copies of themselves," said research associate Naresha Saligrama, PhD, the study's lead author. "This suggested that a specific population of cells were responding."

But what were these T cells responding to? Saligrama first tested the most obvious suspect: MOG. He exposed the cells to 350 peptides derived from MOG. But while MOG caused some T cells to proliferate, there was a group of CD8 T cells that didn't respond to any of the peptides.

So instead, the researchers cast a much wider net: They tested roughly 5 billion peptides. They used a molecular technique known as yeast display to generate an array of peptides attached to individual yeast cells.

"We are crowdsourcing the T cells. We're asking the T cells, as the disease is progressing, what they are interested in," Davis said. "We're not trying to guess or hypothesize what they are recognizing."

Resurrecting the Titanic

The researchers found two peptides recognized by CD8 T cells involved in the disease. To understand the role of these peptides, they injected them into mice before, after or alongside MOG. Since CD8 T cells are mainly known for killing cancerous and infected cells, the scientists expected that activating these cells would worsen disease.

They were wrong. Activating the CD8 T cells by administering the two peptides consistently reduced or prevented disease in the mice. It was the exact opposite of what they'd expected.

Mark Davis

The startling finding forced the researchers to unearth an idea first proposed in the 1970s: that some CD8 T cells are immunosuppressive. After a flurry of initial interest and promising papers, faith in suppressor CD8 T cells sunk once speculation outpaced the actual data.

"Suppressor CD8 T cells did for immunology what the Titanic did for the cruise industry," Davis said.

Davis and his colleagues found that these peptide-activated CD8 T cells killed disease-causing T cells by punching holes in their cell membrane when grown together in a dish. The CD8 T cells were also coated with surface proteins associated with immunosuppression — yet another clue that these cells were in fact suppressor CD8 T cells.

To determine whether their mouse observations held up in humans, the researchers isolated CD8 T cells from the blood of people with multiple sclerosis and healthy donors. They found that people with the disease tended to have large populations of identical CD8 T cells — just like in mice with the analogous disease. It's a sign that CD8 T cells in multiple sclerosis are homing in on something, and Davis' team is now working to determine what these cells are recognizing and if they are suppressive.

The researchers also plan to test if suppressor CD8 T cells are involved in other autoimmune diseases. Previous findings from the Davis lab suggest that a similar mechanism may be at work in celiac disease. These efforts have the potential to shed new light on how autoimmune diseases work and to uncover new therapeutic targets.

"Crowdsourcing T cells is a fundamentally different way to look at disease," Davis said. "This project shows not only the power of this approach but the power to discover new mechanisms."

Davis is the director of the Stanford Institute for Immunity, Transplantation and Infection. He is also a member of Stanford Bio-X, the Stanford Cancer Institute, the Stanford Cardiovascular Institute, the Stanford Maternal & Child Health Research Institute and the Wu Tsai Neurosciences Institute at Stanford.

Other Stanford co-authors of the study are postdoctoral scholars Fan Zhao, PhD, and Ricardo Fernandes, PhD; graduate student Michael Sikora; research assistants William Serratelli and Winnie Yao; bioinformatics analyst David Louis; research associate Xuhuai Ji, MD, PhD; Juliana Idoyaga, PhD, assistant professor of microbiology and immunology; Vinit Mahajan, MD, PhD, associate professor of ophthalmology; Lars Steinmetz, PhD, professor of genetics; Yueh-Hsiu Chien, PhD, professor of microbiology and immunology; and Christopher Garcia, PhD, professor of molecular and cellular physiology and of structural biology.

Researchers from the University of California-San Francisco also contributed to the study.

This research was supported by the Howard Hughes Medical Institute, the National Institute of Allergy and Infectious Diseases, the National Multiple Sclerosis Society and the Simons Foundation.

Stanford's Department of Microbiology and Immunology also supported the work. **ISM**

Three faculty members appointed to endowed professorships

MICHELE BARRY, MD, senior associate dean for global health, director of the Center for Innovation in Global Health, professor of medicine and senior fellow at the Woods Institute for the Environment and at the Freeman Spogli Institute for International Studies, was appointed the Drs. Ben and A. Jess Shenson Professor.

Michele Barry

Barry's areas of interest include ethical issues involving research overseas, clinical tropical medicine, emerging infectious diseases, underserved populations, the climate's impact on health and women's leadership in global health.

The Drs. Ben and A. Jess Shenson Professorship was established in 1998 with a gift from A. Jess Shenson, MD, made in his name and that of his late brother. The professorship was created to support a faculty member in the Department of Medicine whose teaching is related to clinical medicine. After growing up in San Francisco, the Shenson brothers both attended Stanford, where they earned their bachelor's degrees and medical degrees. They practiced together in San Francisco for many years until Ben's death in 1995. Jess died in 2002. The brothers provided financial support to Stanford for scholars and programs in medicine, art, music and Jewish studies.

ANDRA BLOMKALNS, MD, professor and chair of emergency medicine, has been appointed the Redlich Family Professor.

She was appointed as the inaugural chair of the Department of Emergency Medicine in 2018. Her interests include technology development and medical device innovation.

Andra Blomkalns

The professorship was established in 2010 with a gift from Christopher R. Redlich Jr., who at the time was a member of the board of directors of Stanford Hospital and Clinics, now called Stanford Health Care. The professorship was intended for a faculty member in the field of emergency medicine. Redlich is the former president and chairman of MTC Holdings, a port terminal operating company headquartered in San Francisco, which was founded by his grandfather in 1931. His philanthropy is focused in the areas of medicine, conservation, education and science.

Jeffrey Goldberg

JEFFREY GOLDBERG, MD, PhD, professor and chair of ophthalmology at the Byers Eye Institute, has been appointed the Blumenkranz Smead Professor.

His clinical efforts are focused on patients with cataracts, glaucoma or other retinal and optic nerve diseases. His research focuses on neuroprotection and regeneration of retinal ganglion cells and the optic nerve and on the development of stem cell and nanotherapeutic approaches for eye repair.

The professorship was originally called the HJ Smead Professorship in Ophthalmology. The name changed to the Blumenkranz Smead Professorship when Mark Blumenkranz, MD, a professor emeritus of ophthalmology, retired. It was established with gifts from Ann Smead, the Harold J. Smead Trust and an anonymous donor. The late Harold Smead, PhD, served as president, CEO and chairman of Kaiser Aerospace and Electronics Corp. Ann Smead, his widow, is a managing partner of Mill Creek Systems LLC in Vail, Colorado. **ISM**

OF NOTE

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

NEERA AHUJA, MD, clinical professor of medicine, was co-awarded a $1.8 million, five-year Reimagining Residency grant from the American Medical Association. She will lead a Stanford team in collaboration with teams from the Johns Hopkins University School of Medicine and the University of Alabama-Birmingham School of Medicine in a project to generate, implement and evaluate interventions to reduce resident burnout and improve clinical skill. The project will measure modifiable attributes of the training environment that contribute to burnout. The project is part of the association's Accelerating Change in Medical Education Consortium of 37 medical schools.

Neera Ahuja

Todd Alamin

Subhas Banerjee

Philip Beachy

John Boothroyd

Beth Darnall

Miriam Goodman

Ronit Katz

Seung Kim

Feliks Kogan

Ansuman Satpathy

Carolyn Seib

Matthew Strehlow

Lisa Wise-Faberowski

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TODD ALAMIN, MD, was promoted to professor of orthopaedic surgery, effective March 1. He specializes in minimally invasive spine surgery, spinal tumor surgery and reconstructive surgery for adults with scoliosis. His research focuses on diagnostic and therapeutic methods of understanding and treating spinal pathology.

SUBHAS BANERJEE, MD, was promoted to professor of medicine, effective April 1. He serves as the director of endoscopy, and his research evaluates advanced endoscopic procedures in the diagnosis and management of benign and malignant gastrointestinal disease.

PHILIP BEACHY, PhD, the Ernest and Amelia Gallo Professor and professor of urology and of developmental biology, received the bladder cancer research innovation award from the Bladder Cancer Advocacy Network. The two-year, $300,000 award supports novel and creative projects with the potential to produce breakthroughs in the management of bladder cancer. His research seeks to reduce bladder cancer recurrence by identifying and replacing diseased cells that persist in the bladder lining with healthy progenitor cells.

JOHN BOOTHROYD, MD, PhD, the Burt and Marion Avery Professor in Immunology and associate vice provost for graduate education and postdoctoral affairs, was appointed to the academic council of the Schmidt Science Fellows program. He will provide scientific and career mentoring for a group of fellows and make his expertise available to all current fellows and senior fellows.

BETH DARNALL, PhD, was appointed associate professor of anesthesiology, perioperative and pain medicine, effective May 1. She researches digital, brief, low-cost, scalable behavioral medicine treatments for reducing acute and chronic pain and associated burdens for patients, including how to best help physicians and patients successfully reduce chronic pain and long-term opioid use.

MIRIAM GOODMAN, PhD, professor of molecular and cellular physiology, received the midcareer Landis Award for Outstanding Mentorship from the National Institute of Neurological Disorders and Stroke. The award recognizes faculty members who have shown superior mentorship and training. It provides $100,000 to foster career development of additional trainees in her lab, where the research focuses on how skin and its embedded neurons give rise to touch sensation, and how sensory neurons bend without breaking.

RONIT KATZ, MD, clinical associate professor of medicine, has been assigned by the adjutant general of the California National Guard to serve as state surgeon general for the California State Guard. The surgeon general analyzes, drafts, updates and implements medical plans, programs and policies for the California State Guard
Medical Response Forces. A colonel in the California State Guard, Katz will lead the surgeon general's office of the state guard at command section headquarters.

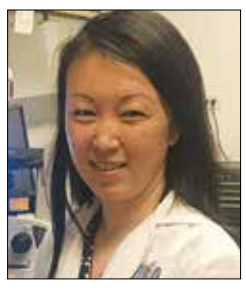
SEUNG KIM, MD, PhD, professor of developmental biology, will serve as a member of the National Institutes of Health Center for Scientific Review's Cellular Aspects of Diabetes and Obesity Study Section for the term that began July 1 and ends June 30, 2023. Members are selected on the basis of their demonstrated competence and achievement in their scientific disciplines.

FELIKS KOGAN, PhD, was appointed assistant professor (research) of radiology, effective May 1. His research focuses on imaging of musculoskeletal function and disease, including developing technologies to detect disease at its earliest stages, and using those new methods to improve patient outcomes.

ANSUMAN SATPATHY, MD, PhD, was appointed assistant professor of pathology, effective July 1. His research focuses on developing and applying genome-scale technologies to study fundamental properties of the immune system in health, infection and cancer.

CAROLYN SEIB, MD, MAS, was appointed assistant professor of surgery, effective April 28. She specializes in endocrine surgery, and her research focuses on the management of endocrine disorders in older adults, including the study of long-term outcomes in elderly people with primary hyperparathyroidism treated with medical or surgical therapy.

MATTHEW STREHLOW, MD, associate professor of emergency medicine, received the lifetime achievement award from the Society for Academic Emergency Medicine/Global Emergency Medicine Academy. This award is given to an academy member who has consistently



Peng Wu

Charles Yu

embodied the academy's ideal of improving the delivery of acute and emergency care through service, leadership, mentorship and academic endeavor.

LISA WISE-FABEROWSKI, MD, was promoted to associate professor of anesthesiology, perioperative and pain medicine, effective April 1. Her research focuses on the neurological effects of anesthesia in young children.

PENG WU, MD, PhD, fellow in pediatric hematology/oncology, was awarded a Damon Runyon-Sohn Pediatric Cancer Fellowship Award from the Damon Runyon Cancer Research Foundation. The four-year, $231,000 award will support her research using new techniques to culture patient-derived cancer cells to understand how abnormal activation of the Wnt signaling pathway drives cell proliferation and irregular differentiation in hepatoblastoma, with the goal of new treatment strategies for liver cancer and other rare tumors.

CHARLES YU, MD, was appointed assistant professor of ophthalmology, effective May 1. He specializes in cornea and refractive surgery. His research involves new technologies for overcoming cornea blindness and ways to improve artificial corneal transplants. **ISM**