**Forgotten immune cells protective in mouse model of multiple sclerosis**

By Jonathan Wosen

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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.

**Major effort launched to harness microbiome for disease treatment**

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

By Erin Digitale

Pivotal treatment response 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, Calif., 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.”

A paper describing the study was published online Aug. 5 in Pediatrics.

“PRT really improved his vocabulary and skills and communication back and forth. It helped us understand what he needs and wants,” the day and come back, he didn’t press his feelings,” she said. “When I would leave for work, 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 and his ability to express his needs, such as by saying “bottle” if he was thirsty.”

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 therapist’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 in the way that could see it and encourage him to say “car.” When he tried to say the word, he was rewarded with the toy.

“He used to not be able to point to something or ask,” Pim said. “He really improved his vocabulary and his ability to express his needs, such as by saying “bottle” if he was thirsty.”

“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.”

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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.

A big surprise

To tackle the problem, Sberro decided to compare potential small-protein coding genes among different microbes and different microbes and different proteins. Those that were identified frequently 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 these genes could be sorted into the functional related groups, or families, likely to be involved in key biological processes such as intercellular communication and manipulation, 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 definitively surprised us all."

The researchers confirmed the genes encoded true proteins by showing they were 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 treating intestinal carcer, 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 Feirmin; postdoctoral scholars Soumya Zilmi, PhD, and Fredrik Edlund, PhD; and Michael Snyder, PhD, professor and chair of genetics.

Researchers from One Codex, the Joint Genome Institute of the Department of Energy, the Alexan- der 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. Depart- ment of Energy and a Damon Runyon Clinical Investigator Award.

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

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 companions, 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 small proteins that they had not noticed 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 and manipulate the composition and hardiness of our microscopic companions.

Researchers at Stanford have found that the bacteria happy and healthy.

Bhatt and her colleagues wondered if answers might lie 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 to control or influence 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, 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 new method

The 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 spray- ing 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 ad- hesion barriers 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, rats that had received no treatment or either of the two commercially available adhesion barriers had formed dense adhesions: Their hearts were con- nected to their chest walls. The rats that were treated with two of the three 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 to human hearts. The initial results were promising.
Fast communication allows microbes to release toxins in unison

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—scouring the inhabitants of the marshy brackish waters. With his eye trained on a large single-cell organism, called Spirostomum, he watched it do something that is now a thing of wonder.

“This is a massive cell, but it contracts in less than a blink of an eye,” said Arnold Mathijssen, PhD, an associate professor in chemistry at the University of California, San Francisco, who treated heart patients at Stanford and lead author of the paper. “It’s possible this is some kind of tension between cells that we’re trying to understand,” said Arnold Mathijssen in biology, but this is really a new kind of signaling between cells, which they were communicating with. 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.

“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 with the hope of growing their own culture 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.

“The first cell contracts and generates a flow, which triggers the second, and that triggers the third,” Mathijssen said. “So you get this propagating trigger wave that passes through the whole colony.”

Mathijssen figured out what triggers the first cell to contract by analyzing an experiment that Prakash and Krishnamurthy had already built for Krishnamurthy’s research.

The researchers next plan to try PNP 1:10 to mayonnaise: PNP 1:10 dissolves and is sprayed onto an organ but instantly reform its consistency. 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.”

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.

Adhesions continued from page 2

human hearts; they find similar results. They found that it is necessary to stick, but not so stiff it detaches from the organs. Appel said. “It was sort of a Goldilocks sweet spot”. He compared PNP 1:10 to mayonnaise: thick, but easily spreadable. The PNP is sprayed onto an organ but then immediately reform its original thickness. The gel also has the ideal tension between stickiness and spreading. “It covers all of the irregular surfaces of the heart, adhering to the tissues, but not to itself,” said Woo, who treat heart patients at Stanford Health Care.

“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 heart patients, but it is made of components that the Food and Drug Administration cleared as safe. For the study, the researchers tested the rats to see if they showed any reaction to the gel; they found 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.

Other Stanford study co-authors are graduate students Amanda Taddeo, Anthony Yu and Gillie Agmon; cardiothoracic surgery residents Alvin Wang, MD, and Michael Paulien, MD; postdoctoral scholars Hector Lopez Hernandez, PhD, and Yoko Tada, PhD; visiting scholar Anton Smith, PhD; research assistant Bhavika Krivchik; graduate student Anahita Eskandari; clinical veterinarian Sam Baker, DVM; former research assistant Camille Hirozaka, medical student Kiah Williams; perfusionist Hunter Bergamasco, Cliffon 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 Cali- fornia Alliance, a Stanford Interdisciplinary Graduate Fellowship and the Ameri- can Association for Thoracic Surgery.

Stanford’s departments of Cardiothoracic Surgery and of Materials Science and Engineering also supported the work.
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 tobacco, 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 cigarettes, 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 cigarette butts, the single most commonly discarded form of litter in the world, defiling just about every kind of natural landscape and built environment, contain toxic chemicals that leach into soil and water supplies.

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 explain.

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, 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-

Researhers 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 somehow 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.

Described in a paper published by the American Heart Association, the device, which is called a NeuroVibe, is a vibrating glove that gently stimulates the wearer’s hand for several hours a day. 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 trying to develop something that we can discover something that really helps stroke survivors.”

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 and hand movement, vision, 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-
Researchers are building glove to treat symptoms of stroke

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

By Grace Hammerstrom

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

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 fine 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 a sense of welcoming 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.”

The committee commissioned several pieces of art for the new Stanford Hospital, all of which have been generously supported by donors. These pieces include specific works grace the entrance plaza, the atrium, the walls of the hospital’s main chapel and the third floor galleria and gardens. Along with the hospital’s art, 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.”

‘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 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-glass finish, the mural shimmers in the chapel’s natural light.

“Rays of Hope” has 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, geometry and his larger-than-life sculpture Buckyball, a 30-foot metal structure featuring three nested spheres. The centerpiece of the new hospital’s entry 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 geometric 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 will create Buckyball with LED light strips, and programmed them to twinkle, blink and slowly shift to create a mesmerizing pattern of light each evening. 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.

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, ashes 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.

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 distinctively walled mural based on a drawing by the late artist Sol LeWitt. He is best known for his bold, colorful, geometric works comprised of streets and curves. In July, two master painters experienced in creating 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. 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 surrounding 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 additional private space for reflection.

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Leonard Weisberg, artist, with the hospital’s glass dome and Liquid Light artwork.
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: genome sequences for 2,308 people from 493 nuclear families affected by autism.

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

What is interesting about these new genes 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.

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 autism-like behaviors, such as Angelman 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.

Identifying this rare syndrome is useful because it helps us parallel 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.

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.

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

Wall: With the help of experts who could find important 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 — say, sending data on an interest email list — 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 no cost to them.

That is really important because without data sharing, replication of findings is not possible. And only the 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.

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What do you think has been the most important thing about this study?

Wall: It’s discouraging for parents of lower-functioning children who have the greatest needs, she said, adding, “This provides a lot of hope.”

We want to continue identifying the most common genetic changes that 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.

“There are at least two children per family affected by autism, 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 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 risk of autism, the total picture of autism vulnerability comes from the combination of inherited risk plus new genetic changes that occur spontaneously in the womb. Inheriting and new variants combine to create the tipping point that manifests in autism.

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 work uncover about autism?

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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.

One of the major goals of this work was to make use of 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 the blood of people with multiple sclerosis.

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“T cells engage 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 suggests that a specific population of cells were responding.”

But what were these T cells responding to? A specific disease-related antigen or some obvious suspect: MOG. He exposed the cells to 350 peptides derived from MOG, which are present on large populations of identical CD8 T cells that didn’t respond to any of the other antigens.

So instead, the researchers cast a much wider net: They tested roughly 5 billion peptides. They used a molecular technologies to search for an array of peptides attached to individual yeast cells. They were looking for specific peptides that were recognized by MOG. Mice with the disease, known as experimental autoimmune encephalomyelitis, develop paralysis just like patients with multiple sclerosis.

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In most cases, researchers don’t know what molecules trigger autoimmune disease. The MOG protein is one of the most obvious targets. “MOG is a molecule that’s present on almost all neurons in the central nervous system, and it’s a very obvious suspect,” said research associate Naresha Saligrama, PhD, the study’s lead author. “This suggests that a specific population of cells were responding.”

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An initiative focused on developing and testing new disease therapies.

The researchers 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 MOG peptides.

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Three faculty members appointed to endowed professorships

MICHÉLE 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 the Freeman Spogli Institute for International Studies, was appointed the Dvs. Ben and A. Jess Shenson Professor.

Barry’s areas of interest include ethical issues involving research overseas, clinical trial methodology, emerging infectious diseases, underdeveloped populations, the climate’s impact on health and women’s leadership in global health.

The Dv. Ben and A. Jess Shenson Professorship was established in 1998 with a gift from A. Jess Shenson, MD, 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.

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, MD, PhD, professor and chair of ophthalmology at the Byers Eye Institute, has been appointed the Blumenkranz Smed 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 Smed Professorship in Ophthalmology. The name changed to the Blumenkranz Smed Professorship when Mark Blumenkranz, MD, a professor emeritus of ophthalmology, retired. It was established with gifts from Ann Smed, the Harold J. Smed Trust and an anonymous donor. The late Harold Smed, PhD, served as president, CEO and chairman of Kaiser Aerospace and Electronics Corp. Ann Smed, his widow, is a managing partner of Mill Creek Systems LLC in Vail, Colorado.