For Stanley Falkow, a legacy of mentorship

By Kathy Zonana

When Stanley Falkow was awarded a National Medal of Science last year at the White House, he was lauded not only for “his monumental contributions toward understanding how microbes cause disease and resist the effects of antibiotics,” but also for a lesser-known, albeit perhaps equally significant, legacy: “his inspiring mentorship that created the field of molecular microbial pathogenesis.”

Over the course of his career, Falkow, PhD, a professor emeritus of microbiology and immunology at the School of Medicine, became known for his generosity and inspiration as an adviser to young researchers trying to forge careers in science. He has mentored more than 100 graduate students and postdoctoral scholars in his lab. Three of them — Manuel Amieva, MD, PhD, associate professor of pediatrics and of microbiology and immunology; Denise Monack, PhD, professor of microbiology and immunology; and David Relman, MD, professor of medicine and of microbiology and immunology — have made their mark on their fields.

Falkow’s influence extends beyond his lab. His former students hired his lab technician in 1984, now, she’s a professor at Stanford.

Although Falkow is quick to deflect any credit, these faculty members are deepening his legacy at Stanford in several ways: in the teaching of microbiology, in research that underscores the impact of microbes on human health, and in big, connect-the-dots ideas that bridge basic science and medicine.

The Robert W. and Vivian K. Cahill Professor in Cancer Research, Emeritus, Falkow “is one of the most generous people with his ideas and with his time and with his energy and of course with all of his other resources as well,” Relman said. “He never has done any of that giving with anything other than obvious evidence of joy. And it’s not just the joy of being a generous person, but the joy of sharing interesting ideas and having such a wonderful job, so that you can’t help but leave his room feeling like we are so lucky to get to think about these interesting questions and work with such great people and try to do useful things.”

But first, how not to mentor

Falkow’s journey to becoming a master mentor began with a mistake. He was in his first faculty job, at Georgetown University, and a former co-worker from Walter Reed Army Institute of Research had, at the urging of Falkow and others, just earned a PhD in a colleague’s lab. “The day he got his degree, he walked into my office and said, ‘Falkow, I hope you’re satisfied, because this is for you and not for me,’” Relman remembered. “I was stunned. And he said, ‘All I wanted to do was go into the lab every day, do experiments and go home, and now my life is ruined because I can’t go home and enjoy it.’”

Falkow would never again be so directive, or push someone toward an aspiration that might not be theirs. “I decided the best thing to do was to just listen,” he said. “And in the years when I listened, I listened very carefully to what my students said, and then I told them to do what they said they wanted to do. And they usually thought I was very wise.”

Amieva recalled visiting Falkow’s office as a postdoctoral scholar to talk about his research. “He would just listen and then he would make some insight that could have several meanings,” Amieva said. “It was almost like some part of him would lead out what he meant and spend the whole day doing it. It’s a technique he uses to make you think through things.”

On the side of microbes

Amieva was first inspired by Falkow during medical school. “I was a little bit disappointed with the classes in medical school; they were very dry and about all these facts, and I remember being a little bit angry about the lack of inspiration,” he said. “And then I took a class from Stanley Falkow.”

See FALKOW, page 6

Popular mouse model of human immune system unsuitable for stem cell studies, researchers find

By Krista Conger

A type of mouse widely used to assess how the human immune system responds to transplanted stem cells does not reflect what is likely to occur in patients, according to a study by researchers at the School of Medicine.

The researchers urge further optimization of this animal model before making decisions about whether and when to begin wide-scale stem cell transplants in humans.

Known as “humanized” mice, the animals have been engineered to have a human, rather than a murine, immune system. Researchers have relied upon the animals for decades to study, among other things, the immune response to the transplantation of pancreatic islet cells for diabetes and skin grafts for burn victims.

However, the Stanford researchers found that, unlike what would occur in a human patient, the humanized mice are unable to robustly reject the transplantation of genetically mismatched human stem cells. As a result, they can’t be used to study the immunosuppressive drugs that patients will likely require after transplant.

The researchers conclude that the humanized mouse model is not suitable for studying the human immune response to transplanted stem cells or cells derived from them.

Technique enhances privacy for genetic-study participants without compromising science

By Krista Conger

It is now possible to scour complete human genomes for the presence of disease-associated genes without revealing any genetic information not directly associated with the inquiry, Stanford researchers say.

This “genome cloaking” technique, devised by biologists, computer scientists and cryptographers at the university, ameliorates many concerns about genomic privacy and potential discrimination based on an individual’s genome sequence.

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The researchers conclude that the humanized mouse model is not suitable for studying the human immune response to transplanted stem cells or cells derived from them.

In an ideal situation, these humanized mice would reject foreign stem cells just as a human patient would,” said Joseph Wu, MD, PhD, director of Stanford’s Cardiovascular Institute and professor of cardiovascular medicine and of radiology. “We could then test a variety of immunosuppressive drugs to learn which might work best in patients, or to screen for new drugs that could inhibit this rejection. We can’t do that with these animals.”

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Infants’ racial and ethnic identities influence the quality of medical care they receive in California’s neonatal intensive care units, a study from the School of Medicine has found.

The study, which examined medical care of more than 18,000 of the state’s smallest babies at 134 California hospitals, was published Aug. 28 in the journal Pediatrics.

The disparities were not uniform: At some California hospitals, infants from vulnerable populations received worse care than white infants, while at others, they received better care than whites. In general, however, the hospitals with the best outcomes for their patients also delivered better care to white infants. In addition, the study found that black and Hispanic infants were more likely than white infants to receive care in poor-quality NICUs.

“The smallest babies

The study used data from the California Perinatal Quality Care Collaborative, which has collected information on 95 percent of premature births in the state. The study included 18,616 babies whose birth weights were less than 3.3 pounds, a category known as very low birth weight, and who were born between the beginning of 2010 and the end of 2014. The research excluded infants born extremely prematurely (before 24 weeks of pregnancy), those who died before 12 hours of age and those with severe congenital abnormalities.

Profit and his colleagues used an index they had previously developed and validated to measure NICU care. To use the index, called Baby-MONITOR, each infant’s medical records are evaluated and scored on nine yes-or-no questions, all of which have been shown in prior research to reflect the quality of medical care. Some questions assess whether patients received aspects of NICU care that are in keeping with standard medical practices for premature babies, such as being examined for an eye disease called retinopathy of prematurity, or receiving steroids before birth to help their lungs. Other questions assess specific medical outcomes, such as experiencing a hospital-acquired infection or growing at a healthy rate. All questions are weighted such that better outcomes produce higher scores.

The analysis then adjusts scores to account for the length of the mother’s pregnancy, whether the mother received prenatal care, whether the baby was from a single or multiple birth, the baby’s 5-minute Apgar score (a quick assessment of the infant’s physical health at birth) and whether delivery was by cesarean section.

Scores were also statistically adjusted to reflect the fact that some hospitals cared for sicker babies, on average, than others. The final score for each hospital, and for each group of patients within a hospital, reflects whether the hospital did the same, better or worse than would be expected in addressing their patients’ medical problems. Scores were calculated separately for white, black, Hispanic, Asian and “other” infants and referenced for each subgroup against whites.

When researchers analyzed the populations of very low birth weight infants in their study, Hispanic infants and those with “other” ethnicity had lower Baby-MONITOR scores than white infants, while black and Asian infants did not have significantly different scores than whites. However, across the state, white infants scored higher on measures of whether standard medical practices were followed. For instance, 89 percent of white infants and 88 percent or Asian infants in the study received steroids before birth to mature their lungs, while 87 percent of black infants and 84 percent of black infants got the same treatment. The difference remained statistically significant after accounting for possible confounding factors.

Black infants had lower rates than white infants of receiving any human milk at discharge — an indicator of worse outcomes — but also had better outcomes in some areas, including faster growth rates and lower rates of chronic lung disease and collapsed lung. Hispanic infants did worse than whites on all components of the score except collapsed-lung rates.

Across NICUs, those that provided the highest quality of care tended to have the smallest disparities between ethnicities; in some, blacks fared better than white infants. As quality scores rose across hospitals, white infants tended to do better.

The researchers also found that although racial and ethnic differences in NICU care were fairly small when examined across California as a whole, some individual hospitals had large gaps in how they cared for infants from different racial and ethnic backgrounds.

Individualizing care

Addressing the disparities will require a nuanced approach, Profit said. “It’s really important for NICUs to individualize care to the patient population they see,” he said.

For instance, Hispanic families who are primarily Spanish-speaking may be experiencing language barriers that make it harder for them to ask questions and act as advocates for their infants. “For them, having access to translation and person who speaks Spanish is really critical,” he said. Hospitals serving a larger proportion of African-American infants may have different issues they need to address.

“There’s a long history of disparity in health care delivery,” Profit said. “If we can get things right early on, that could have a huge long-term effect.”

Other Stanford collaborators on the research are Jeffrey Gould, MD, professor of pediatrics; biostatistician Mihoko Bennett, PhD; Ciaran Phibbs, PhD, associate professor of pediatrics; and Henry Lee, MD, associate professor of pediatrics. Profit, Gould and Lee are members of Stanford’s Child Health Research Institute.

Researchers at Duke University School of Medicine and the University of California-Santa Cruz also contributed to the work.

The study was supported by grants from the National Institute of Child Health and Human Development.

Stanford’s Department of Pediatrics also supported the work.

The next step, Profit said, is to help California’s NICUs identify ways in which they can each make progress in treating all infants more equitably. “Our goal is to develop performance and quality measures for NICUs throughout California so that each can see how well they are performing for infants of different races and ethnicities in comparison to their peers,” he said. The feedback will become part of the work of the California Perinatal Quality Care Collaborative, which organized successful quality-improvement initiatives to help NICUs across the state improve the medical care they deliver.

The researchers are also working with the Vermont Oxford Network, a sister organization that monitors NICUs across the country to provide similar feedback to hospitals nationwide.

“We need to continue to identify vulnerable populations, make sure they get their needs met and find better ways to engage all families in our care,” Profit said.

Hospital care during the newborn period is not the largest contributor to health disparities that may start in infancy, Profit noted, estimating that socioeconomic and biological differences likely make a larger contribution. Nevertheless, that does not mean racial disparities in medical care should be ignored, he added.

“For many of these infants, their time in the NICU sets them on track for their entire life,” Profit said. “If we can get things right early on, that could have a huge long-term effect.”

Cardiovascular Symposium will bring together experts from Stanford, China

By Erin Digitale

Traffic on Santa Clara’s Stephens Boulevard is heavy as a symphony orchestra tunes up. As the traffic rolls by, a bus passes by a McDonald’s through the open sunroof, heading for a university where a symposium on cardiovascular disease is about to begin.

The symposium, held by the Li Ka Shing Center for Learning and Research, runs Sept. 21-22 at the medical school’s Li Ka Shing Center for Learning and Research.

Topics to be discussed include: Advances in cardiac surgery, vascular surgery, percutaneous treatment of coronary artery disease, wireless sensor technology in health care, imaging technologies in cardiovascular disease and the role of stem cells in cardiovascular disease.

The symposium is being held in collaboration with the key cardiovascular research centers across the world: the Mayo Clinic, Stanford, the Cleveland Clinic and Duke University.

The event is being held to facilitate future collaborations between Stanford’s leading cardiovascular research teams and the leading cardiovascular research teams in China.

Cardiovascular disease is the number one cause of death in the United States, with the majority of cardiovascular disease deaths occurring in the aging population.

By Tracie White

The Stanford-China Cardiovascular Research Symposium will take place Sept. 21-22 at the medical school’s Li Ka Shing Center for Learning and Knowledge.

The two-day conference, which is free and open to the public, will bring together a variety of experts in cardiovascular medicine from the United States and China to share knowledge that can advance heart health. The conference aims to foster communication between Stanford’s postdoctoral scholars, clinicians and researchers to share expertise in order to facilitate future collaborations between China’s leading cardiovascular treatment and research institutions and Stanford, said Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute, which is organizing the event.

‘This conference draws cardiovascular experts from many of China’s most esteemed hospitals and universities, offering a valuable opportunity to share knowledge with Stanford and U.S. experts,” Wu said. “This will also be an opportunity to perform for infants of different races and ethnicities in comparison to their peers,” he said. The feedback will become part of the work of the California Perinatal Quality Care Collaborative, which organized successful quality-improvement initiatives to help NICUs across the state improve the medical care they deliver.

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Study on what leads to chronic migraines seeks participants

By Bruce Goldman

Researchers at the School of Medicine are recruiting participants for a clinical trial aimed at finding out why some people who suffer occasional migraine headaches progress to a chronic stage of having them more often than not. Investigators hope to find out why.

The one-year seed grants of up to $75,000 are being awarded to projects jointly led by principal investigators from Stanford and Intermountain Healthcare. The grants will take effect Sept. 1.

The trial is funded by the Sun Star Foundation.

Who experience migraines or other headache types, but also people who don’t have headaches at all to serve as control subjects. “Our understanding of headaches lags well behind that for many other neurological conditions, which is sad since it’s the most common neurologic complaint a doctor will see,” said the trial’s principal investigator, Robert Cowan, MD, professor of neurology and neurological sciences.

“Everyone knows at least someone who suffers with migraine,” said Cowan, who holds the Betty Higgins Family Foundation Professorship in Headache Medicine and is the director of Stanford’s Headache and Facial Pain Center.

Of the 60 million people in the United States who get headaches, he said, 37 million of them get migraines — intense throbbing headaches often accompanied by nausea and/or hypersensitivity to sound and light. Among a substantial fraction of migraine sufferers, this painful experience is preceded by a characteristic aura, often visual, disturbance known as an aura.

Costly condition

Cowan experienced his first migraine at age 5. More typically, though, migraines hit people hardest during their most productive years. There’s an uptick of migraine incidence in the teen years and early adulthood, when people are getting their educations, starting families and building careers.

For as-yet unknown reasons, women tend to have migraines three times as likely as men to suffer from migraines.

The bulk of the estimated $15 billion to $30 billion annual cost of headaches to the U.S. economy is accounted for by loss of work productivity, said Cowan. These people, who experience symptoms more days than not, number in the millions.

For the majority of patients with migraines, the most effective prescriptions are lifestyle recommendations, he said. “Don’t skip meals, keep regular hours and get daily exercise — don’t just sit around.”

Better understanding sought

Why some people are susceptible to migraines and why some — but not others — who do get them become more susceptible over time isn’t well understood, Cowan said.

“The basic question we’re addressing is: Why do some people get occasional headaches while others get headaches with increasing severity and disability? Are chronic migraines just episodic migraines that occur more often? We suspect not,” he said.

The investigators will conduct rigorous analyses of trial participants’ blood, brain function and cerebral spinal fluid in an effort to correlate with migraine susceptibility, severity and frequency.

Participants will be asked to fill out medical questionnaires and report to the Stanford campus for a minimum of two or three roughly one- to two-hour medical visits. (Free parking will be provided.)

The investigators will draw participants’ blood and record their brain activity using functional magnetic resonance imaging and perform lumbar punctures, also known as spinal taps. Participants who agree to undergo fMRI or lumbar punctures will receive compensation of $50 apiece for each procedure.

“If we can find risk factors that predispose some migraine patients’ progression from an episodic to a chronic condition, and use these to identify at-risk patients, it may provide insight into personalized treatments to prevent episodic headaches from becoming chronic,” said Cowan.

Prospective participants who want to learn more about the trial or about their potential eligibility for it are encouraged to contact trial coordinator Bharati Sanjanwala at bharatis@stanford.edu.

The trial is funded by the Sun Star Foundation.
Students design small tools to tackle big scientific challenges

By Nathan Collins

Team Traptasia had a problem: The tiny baby sea anemones they were trying to ensnare are, unlike their adult forms, surprisingly powerful swimmers. They are also, as team members and chemist/engineering graduate student Stanford Hunt put it, “pretty squishy little deformable things.” Previous attempts to trap the anemones with Aiptasia, then a postdoctoral scholar, failed. The team decided to build a microfluidic device to catch coral bleaching.

But Traptasia had to make it work. Cawa Tran, then a postdoctoral scholar, and her research into climate change’s effects on coral bleaching were depending on them. (Sea anemones, it turns out, are a close relative of corals, but easier to study.) And then there was the matter of the team’s grades to consider, along with the outcome of an experiment in the “de-microfluidization” of a powerful set of tools known as microfluidics.

Democratizing science

Team Traptasia was part of a microfluidics course dreamed up by Polly Fordyce, PhD, an assistant professor of genetics and of bioengineering and a Stanford ChEM-H faculty fellow. At the time, she was feeling a bit frustrated.

“Microfluidics has the potential to be the really cool science subject,” Fordyce said. “That’s because microfluidics now has this supercool equipment that would normally fill a chemistry or biology lab bench down to the size of a large wristwatch, saving space and materials, not to mention time and money. They also open up entirely new ways to conduct biological research — trapping baby sea anemones and watching them under a microscope, for example. But making high-quality devices takes expertise and resources most labs don’t have.

“There is this big chasm between the biologists who need the tools and the biologists that want to use them,” Fordyce said. Bioengineers know how to design sophisticated devices and biologists have important questions to answer, but there is little overlap between the two.

To bridge the gap, Fordyce invited biology labs to propose projects to students in her graduate-level microfluidics course. She said, was eager to give students real-world experience while giving labs access to technology they might not have time, money or expertise to pursue otherwise.

In fact, the desire to break down disciplinary boundaries was something that attracted her to Stanford and to ChEM-H in the first place. “One of the reasons that I came to Stanford and to ChEM-H in the first place was something that attracted me to Stanford and to ChEM-H,” Tran said.

One of the reasons that I came to Stanford and to ChEM-H was that interdisciplinary institutes that attempt to cross the boundaries between disciplines, she said.

Students use microfluidic tools.

Ultimately, researchers from four labs took part, including, Tran who was working in the lab of John Pringle, PhD, a professor of genetics. Fordyce will be describing her experiences teaching that class in an upcoming paper, which she hopes will provide a blueprint for people eager to help others make use of microfluidics tools.

Shrinky Dinks vs. Aiptasia

Before linking up with Fordyce’s class, Tran had been working with Heath Cartwright, core imaging director at the Carnegie Institution for Science’s Department of Plant Biology. Together they tried a more do-it-yourself approach involving the children’s toy Shrinky Dinks, an approach first proposed by Michelle Khine at the University of California-Irvine.

The effort did not work. “We got some movies. They were mostly end-of-life movies,” Cartwright said.

If Tran and Cartwright managed to trap Aiptasia, their Shrinky Dink device crushed or twisted the sea anemones apart. So when Fordyce approached Tran about working with her team, Tran said the Team Traptasia — graduate students Selim Bhatre, Hunt, Louai Labanah, Sarah Lensch and Will Van Treuren — and Stanford’s Microfluidics Foundry, they jumped at the chance.

A non-smashing success

Team Traptasia, Tran said, solved her problem “completely.” After several rounds of design, troubleshooting and testing, Team Traptasia built a microfluidic device that kept Aiptasia alive and healthy long enough to study. As a result, the researchers could actually watch the effects of rising water temperature and pollution on living sea anemones and their symbiotic algae — something that has never been done before. Tran, Cartwright and Team Traptasia will publish their findings soon, Tran said.

Other teams have helped labs design devices to study how the parasite that causes toxoplasmosis infects human cells, to trap and study placental cells, and to isolate single cells in tiny reaction chambers for detailed molecular biology studies.

Tran said the device Team Traptasia came up with could provide opportunities for the Pringle lab, as well as research. Now an assistant professor at California State University-Chico, Tran said she’ll be using the device with undergraduates there. “Basically, this device has given me the opportunity to train the next generation of biologists,” Tran said.

“Shrinky Dinks will forever be a metaphor for me,” Cartwright said. “It’s a non-smashing success.”

Democratizing science

The new issue of Stanford Medicine magazine, a theme issue on eyes and vision, includes details of daily life hinge critically on vision, more than 20/200 vision, and left it with 20/40 vision. That’s because microfluidics tools.

The issue also includes an article about Stanford Medicine’s inaugural issue of Health Trends Report, an annual review and analysis of the health care sector. Lloyd Minor, MD, dean of the School of Medicine, explains in the article: “In publishing this report, we hope to show how big data is the most important trend facing the sector and, in the processes, inform and educate the entire medical community — including patients, doctors, the private and public sectors — who are actively shaping the future of health care.”

A young Aiptasia sea anemone ejects eggs (highlighted in blue-green) in response to changing water conditions.

Another additional story includes a feature on the use of the anesthetic drug ketamine to treat obsessive-compulsive disorder; and an essay by bestselling author Joyce Maynard about living through a loved one’s painful death from pancreatic cancer.

The magazine is available online at http://stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at 723-6911.

Stanford Medicine magazine reports on the future of vision

By Rosanne Spector

Many of the strategies being explored at the School of Medicine to protect, improve and restore vision sound seriously sci-fi. Among them: cornea transplants conducted with magnetic fields instead of scalpels, virtual reality workouts to repair damaged retinas, and bionic vision.

The new issue of Stanford Medicine magazine, a theme issue on eyes and vision, includes details about these projects and others pushing the boundaries of biology and technology to help people see.

“Studies show that when it comes to their health, the thing people most worry about, after death, is losing their vision,” said Jeffrey Goldberg, MD, professor of ophthalmology. “We got some movies. They were mostly end-of-life movies,” Cartwright said.

“Young polyps (highlighted in green) are developing in response to changing water conditions.”

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"This year was successful beyond my dreams."
Hadza of Tanzania experience seasonal variation in gut-microbe diversity

By Bruce Goldman

More evidence that our intestinal microbes are profoundly influenced by the foods we eat — or don’t. The gut ecosystems of members of a small group of hunter-gatherers inhabiting Tanzania’s Rift Valley show a strong cyclicality consistent with the population’s seasonally changing diet.

A study led by researchers at the School of Medicine is the first to look at seasonal variations in the gut-microbiome composition, or microbiota, of the Hadza, one of the world’s few remaining traditional hunter-gatherer populations. The research confirms that the Hadza microbiota is more diverse than, and substantially different from, that of industrialized countries’ urban-dwelling denizens.

The study is also the first to show that the microbiota composition and diversity of the Hadza reflects the way in which that this variation corresponds to their seasonally fluctuating dietary intake. And the research suggests that sweeping changes in the average person’s diet over the past 10,000 years could be the key driver in the loss of microbial diversity in the typical modern gut.

Surviving hunter-gatherer populations are the closest available proxy to a time machine we in the modern industrialized world can climb into to learn about the ways of our remote human ancestors,” said Justin Sonnenburg, PhD, associate professor of microbiology and immunology at Stanford.

Sonnenburg is the senior author of the multi-institutional study, published Aug. 25 in Science. Lead authorship is shared by Sonnenburg’s former graduate student Samuel Smits, PhD, and Jeff Leach, director of the Human Food Project in Terlingua, Texas.

The life inside our guts

For more than 15 million years, human beings have co-evolved with thousands of microbial species that take up residence in the lowermost part of the intestine, earning their keep by helping us digest food. These environmental changes have wrought corresponding shifts in our microbial exposures, and in our intestines’ ability to serve as hospitable hosts for these symbionts. But it’s been hard to apportion the relative contributions of technological and societal innovations to the loss of microbial diversity in modern populations.

The new study adds evidence that diet is a major factor.

The Hadza number just over 1,000 people, fewer than 200 of whom adhere to the traditional hunter-gatherer lifestyle, which includes a diet composed mainly of five items: meat, berries, baobab (a fruit), tubers and honey. While Western diets are pretty much the same the world over, the Hadza lifestyle doesn’t include refrigerators and supermarkets. So the population’s diet fluctuates according to the season, of which there are two in the Rift Valley: dry, when meat, baobab and tuber consumption play a relatively larger role; and wet, during which berries, tubers, honey and baobab prevail. (Tubers and baobab are available year-around.)

“The 100 to 200 Hadza sticking to this routine will possibly lose it in a decade or two, maybe sooner. Some are using cell phones now,” Sonnenburg said. “We wanted to take advantage of this rapidly closing window to explore our vanishing microbiota.

Tracking the variation

The investigators collected 350 stool samples from 188 separate Hadza individuals over a roughly one-year period encompassing a bit more than one full seasonal cycle. A thorough analysis of the samples’ microbial contents revealed that the gut microbiota varied seasonally, in harmony with the Hadza dietary intake. In particular, a subset of microbial species’ populations diminished in the wet season, when honey accounted for a significant portion of caloric intake, and rebounded in the dry season, when consumption of fiber-rich tubers peaked.

That made sense, Sonnenburg said. “Our own microbiota can change significantly from day to day, or even within hours, in response to what we’ve been eating.”

Samples collected during the same season, but a year apart, contained essentially identical microbial populations, indicating resilience to transitory dietary disruptions.

More surprisingly, the bacterial species whose numbers diminish to sub-detectable levels in the wet season, only to bounce back robustly in the next dry season, appear to be the same ones that — although shared by hunter-gatherers in locations as diverse as modern-day Africa and South America — are resoundingly absent in the guts of the vast majority of those who populate the industrialized world.

This observed seasonal cyclicality, in combination with results of a previous study led by two of the study’s co-authors, offers a possible hint about the case of the missing microbes.

A 2016 study, published in Nature and led by Sonnenburg and senior research scientist Erica Sonnenburg, PhD, showed that while depriving mice of dietary fiber greatly reduced their gut microbial species diversity, this diversity was restored when the dietary-fiber restriction was lifted. But if this fiber deprivation was maintained for four generations, microbial species that had initially bounced back robustly became permanently lost.

Could this be happening, or could it have already happened, in us?

Fiber’s all that’s left at the very end of our digestive tract where these microbes live, so they’ve evolved to be very good at digesting it,” said Sonnenburg. “The Hadza get 180 or more grams of fiber a day in their food, on average. We average 15 grams per day.”

In addition to the Sonnenburgs, Stanford co-authors include graduate student Carlos Gonzalez; former graduate student Joshua Lichtman, PhD; and Joshua Elias, PhD, assistant professor of chemical and systems biology.

Researchers from the Lawson Health Research Institute and Western University in Ontario, Canada, the University of California at San Diego, the National Institute for Medical Research in Tanzania, and the New York University School of Medicine also contributed to the study.

The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the Emch Family Foundation, the Forrest & Frances Lattner Foundation, the C&D Research Fund and the Discovery Innovation Fund.

Stanford’s Department of Microbiology and Immunology also supported the work.

Traptasia

Continued from page 4

...was successful beyond my dreams, and the reason is that the students in the course were incredibly creative and talented and driven,” Fordyce said. She also credits her graduate student and teaching assistant Kara Brower, who won a teaching award for her efforts. “She went way above and beyond what would be required of a TA and really helped imagine and develop the course,” Fordyce said.

“If you put this forward as a model for people at other schools, that could actually make a difference,” both for students and the labs that could benefit from microfluidics, she said.

Fordyce and Pringle are also members of Stanford Bio-X.
Falkow continued from page 1

"He would come in and tell all these amazing stories about microbes," Amieva continued. "And he would say, 'You know, I am on the side of the microbes.'" Amieva joined Falkow’s lab as a postdoc after earning her PhD in cancer biology and completing a pediatrics residency and a fellowship in infectious diseases. "I realized that a lot of the best science comes from making connections between fields or looking at the same thing from a different focal point," Amieva said. "So postdoc training, he thought, was important for me to study not just one disease but multiple diseases. In my lab, I study how these little microneedles, and it injected a protein into the host cells, and it seemed like a form of communication between the bacteria and the host," Amieva said. "That injection system and the protein it delivered were better. I had a feeling that this was kind of sold the project for me. But I was a little hesitant because I’m a pediatrician; this is a disease of adults.

Soon enough, Amieva found himself on the side of the microbe. "As I started to study it, I realized that this is a pediatric infection," he said. "We acquire it in childhood, and we really don’t know much about this interaction until someone gets sick later on. And then I started realizing, ‘Ok, it’s been in humans since humans began.’ So it’s one of those few microbes that have really co-evolved with humans. The more I think about it, the perfect microbe to study.

"We had to learn more and more about the biology of the host cells and human cells, and it was a difficult transition, but we made it," said Falkow. "And in no small measure thanks to her, because she was the common denominator through all these generations of students, and she was the giver of lore to the lab. It got to the point where if you wanted to know something, you asked Denise.

That said, Falkow was concerned about his lab manager’s future. "She was presenting an interesting hypothesis on the microbiome. But I was worried that the university would not be able to publish, but she was stuck here, and there was no way for her to advance her career," said Falkow. "And the science is the most fascinating. There was no paper, no matter how good that science was, he was not going to publish it, ‘cause he didn’t believe in it. And she’s turning out students who are in their own right successful, and she takes great pride in that.

That, Falkow said, is something she learned from her mentor. "I do think I mostly they nanociling, and now at Stanford’s, and it clearly has worked for him. I give graduate students and postdocs a lot of freedom, but I monitor what they’re doing, and if they’re struggling, I help them. I think it’s best to allow people to be creative on their own. You get the best out of people when you make it clear that you trust them and you respect them.

Curiosity and intuition

Relman used the postdoc in Falkow’s lab for 5½ years, until a faculty position opened up in the Division of Infectious Diseases. "Stanley always used to say he would have to take out adoption papers, because this was going to be a long, long, long story," Relman said. It was a joke, but the familial regard was authentic. "He was warm and direct and funny and genuinely interested in me and in his people and in his role as a mentor," Relman said. "But I realized that he didn’t view that relationship as a hierarchical one at all. It was his creation of an extended community with a family feel."

Relman found the gateway to much of his life’s work one day when he and Falkow attended the weekly clinical conference of the infectious disease division.

In 2016, Falkow received the National Medal of Science for his work studying how bacteria can cause human disease and how antibiotic resistance spreads.

In 2015, he began to use the term "legacy." Falkow will allow that Monack "shares something with me, and I’m very grateful for that." And yet, he emphasized, she has carried on his work in carrying out investigations-host pathogen relationships, using a certain style. "She has her own personality of science," he said. "It’s everything that you look for in a student that you train. You don’t want them to be clones of yourself — I and it doesn’t believe in that. You and she’s turning out students who are in their own right successful, and she takes great pride in that.

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The presenter was Lucy Tompkins, MD, PhD, the Lucy Becker Professor in Medicine and professor of microbiology and immunology. (She’s a Falkow’s lab alumna herself, and now his wife.) She was presenting an interesting case of a disease that clearly seemed to be caused by a bacterium, but no one had been able to grow this organism, no one knew where it came from, and no one knew what it was, and the usual kinds of testing were all negative," Relman remembered. "So Stanley said, ‘You’ve been looking and looking at these clefts of bacteria sitting in the spleen or liver, there’s got to be a way to learn something about these things that doesn’t involve trying to cultivate them.’ So I said, ‘Well, I’m interested.’"

With a couple of well-placed bounces from Falkow, Relman soon found himself

self-collaborating with microbiologists in Indiana who had found a way to reveal the presence of bacteria in soil by cultivating them, and with scientists in the East Bay, one of whom just invented a new method of exploiting the chain reaction technique to amplify DNA. Using a new experimental approach, Falkow and his colleagues identified the bacterium, now classified as Cardiobasillia, that causes the disease, bacillary angiomatosis. It turned out also to cause cat-scratch disease.

"It was just because of Stanley’s curiosity, his willingness to put himself out there and go against the tide about their problem, and then as often is the case with Stanley, he has an idea of where the right direction might be," Relman said. "He might not know the details of how to get it done, but he knows, ‘Head in that direction, you’ll see something that way.’ I have since then found myself and maybe deliberately put myself in the position of being one of relatively few clinicians working in an area of science that is mostly populated by non-clinicians, but who have an interest in understanding the clinical ramifications of the story.”

Relman used the same method on other discoveries, standing up to use it to look at commensals in the human body. Today, that microbiome research is his main focus.

"The reason led to my beginning to do this work on the human microbiome, and that was clearly influenced by Stanley,” he said. “There is now the Thomas C. and Joan M. Merigan Professor. ‘He’d always been interested in commensals. It was his goal, by his own admission, to study every single commensal, and also promoted the general value of curiosity and exploration, so I’m interested in all of that work on the microbiome because of him, and about 15 years ago that became the thing I did.’"

Relman is impressed by Falkow’s ability to collaborate broadly. "David is in full command of at least a cruiser, if not a battleship,” he said. "He walks two lines at a time. It’s the science is the most fascinating. There is no paper, no matter how important, that will have continuing impact in the way that a subsequent generation of people will, if trained especially well or potently, or with sufficient power of science, will in turn bestow that upon their trainees. There are second- and third-generation Stan- ley people now who recognize Stanley’s contribution to the microbiome, which they do science as if not direct means but by verbal inference. I think all of us can only do our best, and I’m happy to had influence the way Stanley has had.”

’A microcosm of my life’

When Falkow looks at the careers of Amieva, Monack and Relman, he sees, "more or less, a microcosm of my life.” Each, he says, "has carried on his own personality. “If David is Darwin walking around the Galapagos measuring beaks, Monack is Darwin walking around the Galapagos enjoying the beauty of the situation,” he said. “Denise is more of a generalist and she studies microbiology — places I didn’t go. She’s a very practical, pragmatic person. And yet, he emphasizes, it all started with him, to the four of us — or any group of us — are together, we’re talking about science,” he said. "And the science is the most fas-
Mouse
continued from page 1

Wu shares senior authorship of the research (along with published Aug. 22, in Cell Reports, with Dale Greiner, PhD, professor in the Program in Molecular Medicine and the Department of Molecular and Human Genetics at the Weizmann Institute of Science; and Leonard Shultz, PhD, professor at the Jackson Laboratory for Mammalian Genomics, in Bar Harbor, Maine). The other significant contributors include colleagues Niguel Kooreman, MD, and Patricia de Almeida, PhD, and graduate student Jonathan Stack, DVM, share lead authorship.

“Although these mice are fully functional in their immune response to HIV infection or after transplantation of other tissues, they are unable to completely reject the stem cells,” said Kooreman. “Understanding how we can overcome this deficiency, is a critical step in advancing stem cell therapies in human.”

“Humanized mice are critical preclinical models in many biomedical fields helping to bring basic science into the clinic, but as this work shows, it is critical to frame the question properly,” said Greiner. “Multiple laboratories remain committed to this by this, and whether we can overcome this deficiency, is a critical step in advancing stem cell therapies in human.”

Understanding stem cell transplants

The researchers were studying pluripotent stem cells, which can become any tissue in the body. They tested the animals’ immune response to human embryonic stem cells, which are naturally pluripotent, and to induced pluripotent stem cells. Although IPS cells can be made from a patient’s own tissues, future clinical applications will likely rely on pre-screened, FDA-approved IPS cell-derived products developed for specific clinical situations, such as heart or liver cells that are ready to be used to bridge a heart attack, or endothelial cells to stimulate new blood vessel growth. Unlike human embryonic stem cells, IPS cells would be reliable and immediately available for clinical use. But because they won’t genetically match each patient, it’s likely the physicians would have to screen and give the recipients immunosuppressive drugs.

The researchers were studying plu- ripotent human stem cells. This work was first developed in the 1980s. Researchers genetically engineered the mice to be unable to develop their own immune system. They then used human immune cells with bone marrow precursor cells to reconstruct the animals’ immune system.

Over the years subsequent studies have shown that the human immune cells were able to survive and integrate into the human thymus and liver and are also implanted into the xenografts. In their current studies colleagues found that two varieties of humanized mice were unable to completely reject unrelated human embryonic stem cells or IPS cells. T cells were able to grow and function normally in the transplanted stem cell grafts. In some cases the immune cells grew rapidly to form cancers called teratomas. In contrast, mice with unaltered immune systems quickly dispatched both forms of human pluripotent stem cells.

The researchers obtained similar results when they transplanted endothelial cells derived from the pluripotent stem cells. A new mouse model

To understand more about what was happening, Kooreman and his colleagues created a new mouse model similar to the humanized mice. Instead of reconstructing the animals’ non-existent immune systems with human cells, however, they used immune and bone marrow cells that were genetically different from the mice to test the hypothesis.

Unlike the humanized mice, these new mice robustly rejected human pluripotent stem cells as well as mouse stem cells from a genetically mismatched strain of mice. In other words, their newly acquired immune systems appeared to be in much better working order.

Although more research needs to be done to identify the cause of the discrepancy between the two types of animals, the researchers speculate it may have something to do with these differing immune systems with human cells, however, they used immune and bone marrow cells that were genetically different from the mice to test the hypothesis.

The immune system is highly complex and there still remains much we need to learn,” said Shultz. “Each roadblock we identify will only serve as a landmark as we navigate the future. Already, we’ve seen recent improvements in humanized mouse models for foster enhancement of human immune function.”

Wu is a member of Stanford Bio-X, the Stanford Cancer Institute and the Stanford Child Health Research Institute. He is also the Simon H. Stertz Professor.

Additional Stanford co-authors are former research assistant Raman Nekhlyudov, and graduate students Sebastian Diecke, PhD, and Veronica Sanchez-Freire, PhD; postdoctoral scholar Ning Yu; and research instructor Elena Mata, PhD; and associate professor of pathology Andrew Connolly, MD, PhD.

The research was funded by the California Institute of Regenerative Medicine, the National Institutes of Health and the Pritzker Family Foundation.
Med X to focus on promoting positive change in health care

By Tracie White

Medicine X, Stanford’s premier conference on emerging health care technology and patient-centered medicine, will return to campus Sept. 15-17.

This year’s conference, which will be held at the Li Ka Shing Center for Learning and Knowledge, will focus on the responsibilities of health care citizenship and how individuals can take action to improve health care in the United States.

“Medicine X 2017 will focus on how we can take action to create the change that we want to see in the health care system and move beyond ideas into action,” said Lawrence Chu, MD, professor of anesthesiology, perioperative and pain medicine and founder and director of Medicine X. “With the current uncertainty in the future of health care, it’s important to stop and consider how each of us might work to create a culture of caring that we can’t start to exist right now.”

Medicine X aims to bring together everyone who plays a role in health care — researchers, patients, providers, designers, technologists and policy leaders — and encourage them to work together to build a framework for health care transformation, Chu said.

This framework, known as “Everyone Included,” is a trademark of Stanford Medicine X and was co-developed with a diverse group of health care stakeholders over the past seven years at the conference.

“In January during President Obama’s farewell speech, he talked about how his future role was going to be as a citizen,” Chu said. “That inspired me to think about how we, as individuals, might consider this role in terms of health care. We hope this conference will give people both the inspiration and the tools and resources they need to take action and create change.”

Keynote speakers include:

• Amy Edmondson, PhD, professor of leadership and management at the Harvard Business School, who will speak on “The importance of creating psychological safety when a patient is a part of a health care team.”

• Ai-jen Poo, a 2014 MacArthur “genius grant” recipient and executive director of the National Domestic Workers Alliance, who will speak on “The new caring majority.”

• Hooman Noorchashm, MD, PhD, a cardiothoracic surgeon and activist, who will share the story of his late wife, Amy Reed, MD, PhD, who was harmed during a medical procedure, and the journey they began to change U.S. medical practices.

Conference sessions will include: community organizing and how to create meaningful and lasting change in health care; the challenges of digital health; and a panel session moderated by ProPublica reporter Charles Ornstein on partnering to develop shared resources for cancer patients.

Events over the three-day conference will also feature presentations and panels on a range of topics, including:

• Ideas and experiences from experts in the disability community on what access means to them and a discussion of exploring ways to encourage providers and institutions to go beyond compliance.

• A discussion on the current state of clinical trials and how to move from serving only the needs of researchers to those of patients who participate.

Registration for Medicine X is available online at medx.stanford.edu. Pre-conference events require separate registration.