INSIDE STANFORD MEDICINE

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A teenager awaiting heart-lung transplant became the first person in in the West to undergo a novel procedure.

Page 5

How Irv Weissman learned to figure things out

By Krista Conger

NORBERT VON DER GROEBEN

Irving Weissman was born in Great Falls, Montana, where he first immersed himself in the pursuit of scientific discovery as a teenager working for the pathologist Ernst Eichwald.

It was 7:15 on a Tuesday evening in early September, and Irving Weissman, MD, needed a birthday cake, stat. His daughter, Rachel, was turning 22 the next day. Fresh from fishing the Bitterroot River, clad in khakis and a long-sleeved beige shirt and in stocking feet, he picked up the phone to begin cajoling a local bakery to rustle up a cake big enough to serve several dozen people.

"You'd think no one in this town wants to make any money," he said, with a wry smile, after being politely rebuffed. Clearly, the rules in Hamilton, Montana, are a bit different than those in Palo Alto, California.

Undaunted, Weissman, 76, the director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, dashed outside to confer with caterers slow-cooking three large prime rib roasts on the ranch's patio. Could they make a cake by tomorrow? Inside, several groups of people sat on couches or discussed their research at tables in the corner of the large living room. Normally, the room sports a floor-to-ceiling view of the stunning Como mountain peaks, known locally as the Three Sisters. But that evening they were obscured by thick smoke from surrounding forest fires still raging in parts of the state.

Weissman, who also directs the Ludwig Center for Cancer Stem Cell Research and Medicine at Stanford, had invited more than 30 members of his laboratory and the lab of his former student Judith Shizuru, MD, to Montana for an annual scientific retreat at the ranch he co-owns with fellow scientists and longtime friends David Baltimore, PhD, and Leroy Hood, MD, PhD. Earlier that day, attendees had presented their research at the nearby Rocky Mountain Laboratories, where lethal diseases such as Ebola, influenza, plague and the lesser-known Rocky Mountain spotted fever are studied. The next day, they would be given the chance to don the protective gear used by researchers at the biosafety level-4 laboratories for a photo opportunity to commemorate their visit.

The yearly gathering has been a tradition since 1992. But Weissman's Montana roots go much deeper.

A scientist is born

A native of Great Falls, Montana, about 200 miles northeast of Hamilton, Weissman is the son of a hardware store owner and the grandson of a fur trader who emigrated from Russia in the early 1900s to avoid being drafted by the czar during the First World War.

When Weissman was about 10, a teacher gave him a copy of *The Microbe Hunters*, by Paul de Kruif, which fascinated him. He recounted the experience a few days before the retreat at a talk celebrating the 60th anniversary of the McLaughlin Research Institute in Great Falls, where he first immersed himself in the pursuit of scientific discovery.

"From that book, I got an idea of what a life in science might be like," said Weissman. "The microbe hunters were trying to figure out what caused infectious disease. They not only worked out what happened, but immediately applied it to medicine."

Shepherding scientific discoveries into the clinic would prove to be the touchstone of Weissman's career. As a high school student, he helped perform experiments that led to the first successful skin and organ transplantations in patients. As a Stanford faculty member, he was the first to identify and isolate human blood-forming stem cells responsible for the immune system, research that laid the foundation for possible new treatments for cancer, blood diseases and organ rejection.

He also helped devise and promote California Proposition 71, which was enacted in 2004, creating the California Institute for Regenerative Medicine to funnel about $3 billion to stem cell researchers in the state after President George W. Bush restricted federal funding to the field.

Along the way, Weissman learned many valuable lessons.

"I've found in my career that if you don't do it, nobody is going to do it because nobody understands the field like you do," he said. "Pharmaceutical companies make business decisions. If there's a drug that

See WEISSMAN, page 6

Some stage-2 colon cancer patients may benefit more than others from chemo

By Krista Conger

Stage-2 colon cancer patients whose tumors lack a particular protein may benefit from the use of chemotherapy after surgery, according to a retrospective study by researchers at the School of Medicine. Previous studies have suggested that chemotherapy given to stage-2 patients had limited benefit.

The study was published Jan. 21 in *The New England Journal of Medicine* along with two editorials describing its significance.

The researchers categorized colon cancer patients based on the presence or absence of a protein called CDX2, which is found in mature colon cells. In these cells, CDX2 helps to control the expression of other genes that drive colon cell specialization. The researchers found that about 4 percent of people with colon cancer have tumors that don't express CDX2. In an initial study of 466 patients with any stage of colon cancer, only about 41 percent of those with cells lacking CDX2 lived disease-free for five years after treatment, compared to 74 percent of those with CDX2 in their cancer cells.

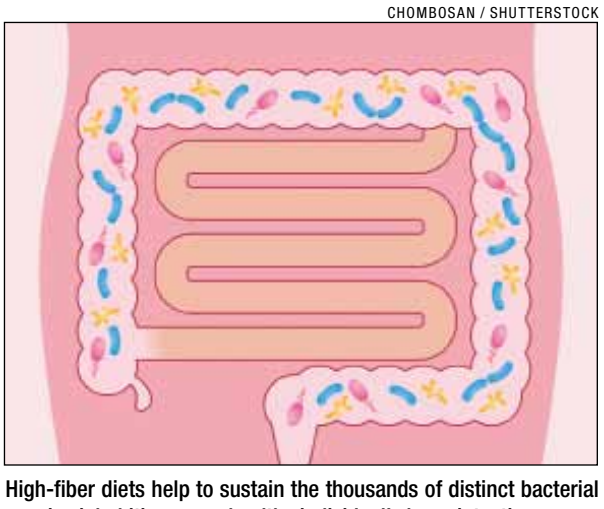
But the researchers iden-

See COLON, page 4

Low-fiber diet may irreversibly deplete gut bacteria populations over generations

By Bruce Goldman

CHOMBOSAN / SHUTTERSTOCK



High-fiber diets help to sustain the thousands of distinct bacterial species inhabiting every healthy individual's large intestine.

A study by School of Medicine investigators raises concerns that the lower-fiber diets typical in industrialized societies may produce internal deficiencies that get passed along to future generations.

The study, conducted in mice, indicates that low-fiber diets not only deplete the complex microbial ecosystems residing in every mammalian gut, but can cause an irreversible loss of diversity within those ecosystems in as few as three or four generations.

Once an entire population has experienced the extinction of key bacterial species, simply "eating right" may no longer be enough to restore these lost species to the guts of individuals in that population, the study suggests. Those of us who live in advanced industrial societies may already be going down that path.

The proliferation of nearly fiber-free, processed convenience foods since the mid-20th century has resulted in average per capita fiber consumption in industrialized societies of about 15 grams per day. That's as little as one-tenth of the intake among the world's dwindling hunter-gatherer and rural agrarian populations, whose living conditions and dietary intake presumably most closely resemble those of our common human ancestors, said Justin Sonnenburg, PhD, associate professor of microbiology and immunology and senior author of the study, published Jan. 13 in *Nature*.

Suboptimal diets

Virtually all health experts agree that low-fiber diets are suboptimal. Probably the chief reason for this is that fiber, which can't be digested by human enzymes, is the main food

See BACTERIA, page 7

5 QUESTIONS

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

Robert Cowan on treating, managing headaches

Robert Cowan, MD, is the founding director of the Headache and Facial Pain Clinic at Stanford Health Care. Its doctors help patients prevent and manage their headaches, working in collaboration with colleagues at the newly opened Stanford Neuroscience Health Center. Cowan, a clinical professor of neurology and neurological sciences, founded the headache clinic in 2011. He is board-certified in pain medicine, neurology and the neurological subspecialty of headache medicine. He holds several nationally elected positions, including chair of the section on chronic daily headache for the American Headache Society. Cowan brings a special motivation to his work: He has managed his own migraines for decades. Recently, Cowan spoke with writer Sara Wykes.

NORBERT VON DER GROEBEN

Robert Cowan brings a special motivation to his work: He has managed his own migraines for decades.

1 Are there different sorts of headaches?

COWAN: Headache is very common: Every year, more than 90 percent of people in the United States experience some type of headache. Tension-type headache is the most common, and 70 percent of people have them at one time or another. The American Migraine Foundation estimates about 12 percent of people in the United States — about 37 million — suffer from migraines.

Sinus problems only occasionally cause headache, no matter what TV ads for decongestants and allergy and cold remedies may say. Studies show that most sinus headaches are actually migraines. Headaches that do not respond to treatment of allergies are probably migraine or tension-type headaches, or they are related to overuse of pain medicines.

2 What's the difference between migraines and other types of headaches?

COWAN: A migraine is much more than a headache. It occurs on average one to four times a month. Unlike a tension headache, it is often accompanied by nausea or vomiting. Its pain is intensified by physical activity and is so severe it interferes with daily activities. About 30 percent of migraineurs — people with migraine — have a warning that consists of neurologic signs, or auras, they experience before the migraine episode begins. The most commonly experienced aura is visual, during which patients see small, colored dots, flashing bright lights or multicolored zigzag lines that may form a shimmering crescentlike shape. Sometimes there are blind spots in the visual field.

Aura symptoms last for 20 to 30 minutes. They are followed within five to 60 minutes by the headache. An aura shorter than five minutes may be something else, so we do not diagnose a patient with short auras as having migraine with aura. Aura symptoms that last more than one hour may be a sign of other neurological problems and should be brought to a physician's attention. The headache that follows the aura is similar to a migraine headache without aura but often milder in intensity.

ALLIANCE / SHUTTERSTOCK

3 Why do some people get headaches and others do not?

COWAN: Migraine seems to run in families, very often on the mother's side. Migraine headache is three times more common in women than in men. That increased risk emerges in women when puberty begins and decreases after menopause.

Genetics can also hardwire us to get headaches. That we can't control, but environment also plays a big role. A headache may come after intense exercise at high altitude or with severe dehydration and high temperature. Some of us are just more sensitive to environmental changes, either in the external environment — too much sun, for example — or in our internal environment, from a drop in estrogen levels or a change in sleep pattern. People who are not headache-prone do not usually get headaches under stressful conditions. However, those who are prone to headache often experience headache when under stress or during the letdown period, the time after a stressful period has passed.

4 How often can I take pain medicine for headache?

COWAN: I chose to enter this field more than 25 years ago because people with migraines and other severe headaches know how disabling they are and because I wanted to offer treatment that was multidisciplinary, that was more than stronger and stronger medication. The vast majority of headaches should not be treated with opioids or any other pain medications. It depends upon what kind of medicine you are taking, of course, but a good rule of thumb is not to take any pain medication more than two days in any week, and no more frequently than recommended on the label or as prescribed.

If you need more medication to control pain, you should consult a physician. Overuse of acute medications can actually increase the frequency of your headaches. Headaches can be worsened by overusing off-the-shelf and prescription medications: analgesics, barbiturates, caffeine and ergotamine tartrate. The simple solution would be to stop overusing pain relievers. But it isn't that easy. Most patients with analgesic rebound who have tried to stop overusing pain relievers have found that their headaches got worse before they got better. Their headaches typically became more intense within four to six hours after stopping the medication and were at their worst within one to two days. This worst period may last for two to three weeks. If this describes you and you have not already consulted a physician, now is the time.

5 What can I do to avoid getting headaches?

COWAN: A good headache-management plan, especially if you experience migraines, starts with observation. We encourage our patients to take note and observe their own patterns of behavior and identify the things that contribute to headaches. Patients may notice they have certain symptoms that appear before a headache begins. Irritability, lethargy, yawning, neck stiffness and a food craving or aversion may be pre-headache signals to note.

A great way for those patients who suffer from chronic headaches to get started is with a diary to record headache frequency and severity, time of onset and similar information for a month or three. You may begin to see patterns that were not readily obvious when you relied on your memory to analyze your headaches. Share your information with your doctor. There are several apps, computer programs and paper diaries available to document your headache history. **ISM**

Medical school opens a new office to help faculty with grant applications

By Kris Newby

While applying for a research grant may sometimes feel like buying a lottery ticket, now faculty at the School of Medicine can improve their odds by taking advantage of resources provided by the new Stanford Research Development Office.

The office's director, Michael Helms, PhD, MBA, is eager to assist faculty researchers with a variety of grant-related tasks. Services provided include identifying funding opportunities, fostering collaborative work, editing proposals, managing the assembly of large proposals and interfacing with sponsors and university liaisons.

Initially, the office will focus its efforts in three areas:

• Large multi-investigator, multidisciplinary grant applications that support School of Medicine centers and programs.

• Multi-investigator grants focused on the school's priority initiatives, such as precision medicine and big data.

• Grants for early-career assistant professors who are writing proposals for their first independent research projects.

Over time, Helms hopes to add training programs on grant writing for National Institutes of Health R01 and career development awards, team building and faculty development. These resources are funded through the office of the senior associate dean for research.

Helms previously worked in the Department of Anesthesiology, Perioperative and Pain Medicine, where he helped the department move from No. 16 in 2009 to No. 2 in 2013, as measured by the amount of NIH funding it received each year compared to other anesthesiology departments nationwide. (In 2014, the department's ranking stood at No. 4.)

He has also been a principal investigator on his own NIH small-business grant and has served as an ad hoc member of an NIH study review section.

Helms said he feels his marketing experience has made a difference in the past proposals that he's worked on. "I put on my MBA hat and help investigators present their ideas in the best possible light," he said. "My goal is to get grant reviewers excited about our research proposals."

To begin the grant application process, contact Helms at mkhelms@stanford.edu or 723-4526, or Sandra Holden, PhD, grant development officer, at srholden@stanford.edu or 724-5345.

To learn more about the grant submission process at Stanford, visit https://doresearch.stanford.edu/research-scholarship/about-proposalapplication-and-award-process. **ISM**

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STANFORD MEDICINE

VANTAGE POINT

one in an occasional series of essays written by faculty and staff

We don't just need precision medicine; we need precision health

By Lloyd Minor

We are coming up on one year since President Obama, in his State of the Union address, committed the nation to a $215 million investment in precision medicine. Since then, we have seen many breakthroughs in the development of therapies tailored to individual patients to treat the deadliest of diseases. Recently we heard the remarkable story of President Carter's advanced cancer in remission from a new immunotherapy treatment. Developments like these give us all hope that we can beat the most difficult medical conditions facing humankind.

I share those high hopes, but I can't help but think that we should aim even higher. If the amazing scientific advances of recent years can help us more effectively treat disease based on individual factors, shouldn't we also put them to work by helping us keep people from getting sick in the first place?

> "We really are on the brink of an amazing transformation in how we approach medicine."

The vision would be to go beyond precision medicine: instead of a frantic race to cure disease after the fact, we can increasingly focus on preventing disease before it strikes. By focusing on health and wellness, we can also have a meaningful impact in reducing healthcare costs. At Stanford, we call this idea precision health, where we focus on helping individuals thrive based on all the factors that are unique to their lives, from their genetics to their environment.

Bringing the promise of precision health to patients will require a fundamental shift in our view of medicine, one which combines two seemingly different approaches — high tech and high touch.

Start with data. Progress in health care has always been based on a crude assessment of accumulated data. We see that something works for one patient, so we try it on a few more and observe what happens. That's all the clinical trials process is, really. But in the past few years, the amount of available data about health care has exploded, to the point where it can be overwhelming.

To take full advantage of these breakthroughs, doctors must add a working knowledge of data science to the natural sciences that have traditionally been the focus of our professional training. Doctors must increasingly be data specialists (and perhaps genomic specialists) and assess large pools of information through the lens of the individual patient.

However, understanding data is not enough. With the advent of digital health devices and online medical websites, more than ever, people have become active managers of their own health and demand a more consumer-friendly health-care experience.

To be truly effective in building a culture of health and disease prevention, physicians need to return to some of the wisdom of our predecessors. We need to recognize that through the intimate bonds we form with our patients when we perform hands-on examinations and listen to their concerns with empathy, we enact a time-honored ritual and gain a different type of critical information than what we can garner from lab tests and radiological scans. This kind of rich, nuanced data — what is important to our patients, what they fear, how their symptoms manifest and how they feel — must also factor into a truly holistic approach to health care.

Lloyd Minor

Increasingly, medical schools are collaborating with engineering, computer science and business innovators throughout Silicon Valley to incorporate the latest developments in their respective fields into medical training and practice. From detailing the human immune system, to finding new applications for drugs, to deciphering autism in children or monitoring pandemic strains with the help of social networks — students are learning how to harness data to improve human health.

Physicians are also partnering with the top minds in Silicon Valley to not only gather data but to better understand how to use it. Stanford, for instance, is collaborating with Google Life Sciences to collect anonymous genetic and molecular information to create what will be the most complete picture of a healthy human being.

We've also launched Presence, a center to foster research, dialogue, and collaboration across Stanford's seven schools to improve the clinical experience for our patients, providers, and families in our hospitals and clinics. Led by Dr. Abraham Verghese, Presence builds upon the Stanford Medicine 25 program, which provides hands-on sessions to emphasize bedside physical exam skills to make sure all of our doctors — from those just entering training to those who have been in practice for decades — maintain a strong bond with patients, make the obvious diagnoses when such signs are written on the body, and use technology judiciously to ensure patients get the care that is right for them.

We really are on the brink of an amazing transformation in how we approach medicine. But we can only go as far as our vision allows us to. I hope President Obama will use this year's State of the Union address to set our sights higher. Because when it comes to health, we must think as big as we can — not just about treating disease, but about making and keeping people healthy. ISM

Lloyd Minor, MD, is the dean of the School of Medicine. This piece was originally published Jan. 6 in Forbes.

Conversations in Global Health to feature former NBC News chief medical editor Nancy Snyderman

Physician, author and former broadcast journalist Nancy Snyderman, MD, will share insights from her storied career covering global health and medicine in a conversation Jan. 27 with Paul Costello, Stanford Medicine's chief communications officer.

Nancy Snyderman

The event, which is free and open to the public, will begin at 5 p.m. in room 320 of the Li Ka Shing Center for Learning and Knowledge.

Snyderman will soon join Stanford as a consulting professor in the School of Medicine. She is the former chief medical editor at NBC News and previously worked as a consumer education executive at Johnson & Johnson and as a medical correspondent at ABC News.

She has reported on wide-ranging issues from all over the globe and has earned some of broadcast journalism's most distinguished honors, including Emmy Awards and Edward R. Murrow Awards.

She began her career as a head and neck surgeon, one of the first women in the United States to specialize in the field, and her medical work has been published extensively in peer-reviewed journals.

Snyderman's discussion is part of the Conversations in Global Health seminar series, organized by Stanford's Center for Innovation in Global Health. ISM

Memorial for Herbert Schwartz set for Feb. 5

Members of the Stanford community are invited to attend a celebration of the life of Herbert Schwartz, MD, from 4:30-6:30 p.m. Feb. 5 at the Stanford Golf Course clubhouse.

Schwartz, a professor emeritus and former chair of pediatrics, died Nov. 13. He was 89.

Those planning to attend the event are encouraged to notify Sara Heller at ssheller@stanfordchildrens.org.

Donations in Schwartz's memory can be made to Lucile Packard Children's Hospital Stanford at http://www.supportlpch.org. ISM

What matters to scientist Lucy Shapiro

By Becky Bach

Fasten your seatbelt: Developmental biology professor Lucy Shapiro, PhD, is driving, and we're zooming through her achievement-packed 40-year career in less than an hour.

Speaking Jan. 13 as part of the "What Matters to Me and Why" series hosted by the Stanford Office for Religious Life, Shapiro, who holds the Virginia and D. K. Ludwig Professorship, said the topic prompted her to ponder why she was so passionate about the world of molecules and cells, a world invisible to most people.

> "My love and passion for the scientific world is spiritual."

Lucy Shapiro

To figure it out, Shapiro said she had to think back to when she was 13, applying for high schools. After consulting with her parents, Shapiro decided to apply for one of New York City's elite public schools that focused on art and music. Unbeknownst to her parents, however, she decided she wasn't going to take the exam in music as planned. Instead, she checked out a book on drawing from the library, taught herself to draw and passed the entrance exam by producing a portfolio of art.

"That was really a defining moment. I learned I could change the trajectory of my own life by some action," she said.

Discovering true love

With that lesson firmly engrained — and with some well-timed assistance from mentors — Shapiro was off. There were detours, of course. Her senior college thesis was on Dante — interesting, Shapiro said, but "it didn't make my heart sing."

When prompted to go back to school and take an organic chemistry course, Shapiro discovered her true love.

"It sounds corny, but it was like the sky cleared. [Chemistry] was the most beautiful thing I had ever seen. It was clear that was how my mind worked," Shapiro said.

She went on to make discoveries about the three-dimensional development of cells, compounds called RNA polymerases and many other aspects of molecular biology that advanced the field, along the way mentoring scores of students and budding scientists. Her awards are numerous and include the prestigious National Medal of Science.

Now, she's particularly passionate about the threat posed by pathogens, which are rapidly outevolving the drugs available to rein them in. In response, she has helped found two pharmaceutical companies and is an active public speaker.

During her talk she offered numerous words of wisdom, including:

- On discoveries: "It's just indescribable when you discover something. It can be little, it doesn't have to be earth-shattering. It is so exciting."
- On spirituality: "To me, science is religion. My love and passion for the scientific world is spiritual."
- On her career: "These past 40 years have just been beautiful. I still can't wait to get into the lab each morning." ISM

Colon

continued from page 1

NORBERT VON DER GROEBEN

Michael Clarke and his colleagues found that stage-2 colon cancer patients with a particular gene-expression pattern may benefit from chemotherapy after surgery.

tified another important distinction between the two groups, particularly in those with stage-2 disease: Patients whose tumor cells didn't express CDX2 were much more likely to benefit from chemotherapy in addition to surgery than were people with CDX2-positive tumors. About 91 percent of patients with CDX2-negative tumors treated with chemotherapy in addition to surgery lived disease-free for five years versus about 56 percent of those who did not receive chemotherapy. Previous studies that did not distinguish between CDX2-positive and CDX2-negative cancers suggested that chemotherapy provided little additional benefit to stage-2 colon cancer patients.

"We've learned that a patient group that formerly was not known to need adjuvant chemotherapy may, in fact, benefit from this treatment. Conversely, it may be possible to identify those patients who could avoid the toxic side effects of chemotherapy," said Michael Clarke, MD, professor of medicine and the Karel H. and Avice Beekhuis Professor in Cancer Biology.

"This research is one of the first examples of how we can use our growing knowledge of stem cell biology to improve patient outcomes."

The retrospective study looked at gene expression in cancer cells and tissues from over 2,000 patients whose treatment courses and outcomes were known. The researchers emphasize that a randomized, prospective clinical trial is necessary to further confirm the results before clinical changes are codified.

Clarke, who is also a member of the Stanford Cancer Institute and the associate director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, is the senior author of the study. Former instructors and Siebel fellows Piero Dalerba, MD, and Debashis Sahoo, PhD, share lead authorship of the study. Dalerba is now an assistant professor of pathology and cell biology and of medicine (Division of Digestive and Liver Diseases) at Columbia University, and Sahoo is an assistant professor of pediatrics and of computer science at the University of California-San Diego.

Stem cell, cancer connection

Clarke and his colleagues have been studying the connection between stem cells and cancer for several years. For this study, Dalerba and Sahoo sought to devise a way to identify colon cancers that were more stem-cell-like, and thus likely to be more aggressive. They looked for a gene that was expressed in more mature cells but not in stem or progenitor cells. They did this by using a novel bioinformatics approach that drew on their knowledge of stem cell biology to identify developmentally regulated genes important in colon tissue maturation.

Because they knew from previous research by Dalerba in the Clarke laboratory that stem and immature colon cells express a protein called ALCAM, Dalerba and Sahoo looked for genes whose protein product was negatively correlated with ALCAM expression. "We reasoned that those proteins would likely be involved in the maturation of colon tissue and might not be found in more aggressive, immature cancers," Sahoo said.

Finally, to ensure their results would be useful to doctors, the researchers added another criterion: The gene had to make a protein that was easily detectable by an existing, clinical-grade test.

The screening technique identified a promising candidate: the CDX2 protein. "We chose CDX2 because it was the only candidate that was already used as a diagnostic biomarker in the clinic," Dalerba said. "However, we were also intrigued by the fact that CDX2 is a master transcription factor controlling the expression of many differentiation genes in colon epithelial cells."

When they separated colon cancer cases into those with cells that either did or did not express CDX2, they found a marked difference in both five-year, disease-free survival rates and in response to chemotherapy.

Data sharing and collaboration

"The CDX2 protein plays a role in the differentiation of the intestinal epithelium," said Clarke, who is also deputy director of the Ludwig Center for Cancer Stem Cell Research and Medicine at Stanford. "The novel bioinformatics analyses used in this paper links its expression to more differentiated cells in colon cancers. We found that patients whose cancers lacked CDX2 expression, which suggests that their tumors have a high proportion of cancer stem and progenitor cells, had a much worse prognosis. However, their outcomes improved significantly if they had received chemotherapy as part of their treatment."

The study is hailed in an accompanying editorial in the journal as an endorsement of data sharing and collaboration among many different research groups. The Stanford researchers used information stored in the National Center for Biotechnology Information's Gene Expression Omnibus database to identify CDX2. Tissue samples were provided by the Cancer Diagnosis Program of the National Cancer Institute, the National Surgical Adjuvant Breast and Bowel Project and the Stanford Tissue Microarray Database.

"A major question in the cancer field is whether the study of cancer stem cells can lead to increases in survival for cancer patients. This research is one of the first examples of how we can use our growing knowledge of stem cell biology to improve patient outcomes," Clarke said.

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

Stanford co-authors of the study are former research assistant Pradeep Rajendran; former graduate student Stephen Miranda; former postdoctoral scholars Shigeo Hisamori, MD, Tomer Kalisky, PhD, and Erna Forgo, MD; project coordinator Jacqueline Hutchison; lab manager Dalong Qian, MD; medical student Nate Wilcox-Fogel; postdoctoral scholar Xiangqian Guo, PhD; pathology professor Matt van de Rijn, MD, PhD; and professor of medicine George Fisher, MD, PhD.

The research was supported by the National Comprehensive Cancer Network, the National Institutes of Health, the Siebel Stem Cell Institute, the Thomas and Stacey Siebel Foundation, the Virginia and D.K. Ludwig Fund for Cancer Research, the California Institute for Regenerative Medicine, the Department of Defense, the Bladder Cancer Advocacy Network and BD Biosciences.

Stanford's Department of Medicine also supported the work. **ISM**

Children's hospital physicians identify mysterious illnes

By Ali Koide

"He was so handsome and so big! He was a little tank," Shannon Catalano said, recalling the joy she felt the first time she and her husband, Steven Catalano, held their youngest son just one year ago. "I immediately knew his name was Wyatt James."

But then, she noticed the odd bumps and blisters covering Wyatt's body from head to toe.

"You can hold him for just a minute," a nurse told them. "But we need to take him to the neonatal intensive care unit."

What should have been one of their family's happiest moments quickly turned somber as they feared the seriousness of Wyatt's condition. The dermatology team suspected it could be a skin disease, but they couldn't know for sure.

COURTESY OF THE CATALANO FAMILY

Wyatt James Catalano, who turned 1 in October, was diagnosed with diffuse cutaneous mastocytosis, a disease of the white blood cells.

'I wanted to cry'

Wyatt needed to be transferred to Lucile Packard Children's Hospital Stanford.

"I wanted to cry as I thought about the fact that his first drive was in an ambulance to another hospital, instead of home with us," Shannon said. "As a mom, we always do whatever we have to do in order to take care of our littles. I didn't care that I had just given birth and was still healing — so long as I could be with my sweet Wyatt."

A special transport team came to bring the newborn to the children's hospital, whose specialists quickly got to work. The next few days were excruciatingly slow as Wyatt endured countless tests to rule out different diseases.

Rare disease

Finally, after six days of poking and prodding, the diagnosis came: diffuse cutaneous mastocytosis, a disease of

Teen awaiting heart-lung transplant first in West to undergo novel therapy

By Samantha Dorman

2016 is starting off a whole lot better than last year did for 14-year-old Oswaldo Jimenez of Salem, Oregon.

Oswaldo was diagnosed with pulmonary arterial hypertension at age 9. In early 2015, his heart and lungs were failing, and a heart-lung transplant seemed to be his only real hope for survival.

Oswaldo was referred to doctors at Lucile Packard Children's Hospital Stanford and Stanford Children's Health, one of America's leading centers for pediatric organ transplant. There, physicians determined that Oswaldo would indeed need a transplant, but that he could return home to Oregon to await notification of donor organs. But in the spring, Oswaldo's condition rapidly worsened. He was admitted to a local hospital and emergency airlifted to Packard Children's in May.

What happened? The pulmonary arterial hypertension made it hard for blood to flow properly through Oswaldo's lungs, where blood picks up oxygen for the rest of the body. "The high blood pressure in his lungs was requiring his heart to pump harder and harder," explained pediatric cardiologist Jeffrey Feinstein, MD, director of the Vera Moulton Wall Center for Pulmonary Vascular Disease and head of the hospital's pediatric pulmonary hypertension program. "This eventually caused his heart to fail."

"When we initially evaluated him a few months earlier, he had very few symptoms; when he returned, he could only walk a short distance before getting breathless," added Feinstein, who is also a professor of pediatrics in the School of Medicine and the Dunlevie Family Professor of Pulmonary Vascular Disease. "The pressure in his lungs also caused two episodes of pulmonary hemorrhage. This bleeding into the lungs can be fatal."

Leader in multi-organ transplant

Combined heart and lung transplants are so rare that only 24 were performed in the United States in 2014. Stanford has long been a national leader in multi-organ transplantation, performing the world's first successful combined heart-lung transplant, on an adult, at Stanford Hospital in 1981.

Listing Oswaldo for transplant was just the beginning. Care teams wanted to ensure his failing heart and lungs could keep going until donor organs were available. They needed to perform what is referred to as a "bridge-to-transplant" solution, one that would sustain Oswaldo's organs until transplant could be done.

"An integral element to success for children awaiting lung transplants is to keep them moving around," said pediatric pulmonologist Carol Conrad, MD, director of the pediatric lung and heart-lung transplant program at the children's hospital and an associate professor of pediatrics. "Being in good shape helps to make them good candidates for the transplant operation. Pre-operative debilitation leads to prolonged recovery period post-op and a poorer outcome in the long run."

A novel procedure

It was then that doctors decided to try a novel procedure, one that would enable Oswaldo to be mobile. Called a pulmonary artery to left atrial shunt, it was a surgery that had been used only a dozen times in patients nationwide. It would reduce the workload on his failing heart, and allow Oswaldo to stay mobile and help oxygenate his blood while awaiting transplant.

"He was so critically ill, and it was a very risky procedure; he was at high risk of cardiac arrest when being put to sleep for the surgery," said Katsuhide Maeda, MD, surgical director of lung and heart-lung transplant program and a clinical assistant professor of cardiothoracic surgery. "But essentially, this shunt established a 'lung' that served to oxygenate his blood as it flowed through a box outside of his body. Since the device was reasonably small, it allowed him to stay awake and mobile while awaiting transplant."

For parents Carmen Hernandez and Martin Jimenez, it was a difficult decision to go forward with this novel procedure, but there were no other options — and they trusted the team.

"We weren't given any hope until we came here," said Oswaldo's mother, Carmen Hernandez, via a translator. "This seemed to give him the best chance to live."

How it's done

The procedure involved the insertion of a tube that redirected blood away from Oswaldo's lungs into the oxygenator. This, in turn, provided oxygen to the blood and then returned it to his body, with his own heart providing the pump.

The shunt device has been shown to sustain patients' lives for several weeks to six months, depending mostly on whether complications such as bleeding, blood clots or stroke arose.

On July 12, Oswaldo made history by becoming the first child in the western United States to undergo this treatment. Then, just one week after receiving the shunt, donor organs became available. Oswaldo received his heart and lung transplant on July 19.

"We are so, so thankful for organ donation," Carmen said. "During another family's time of incredible grief, they gave my son the ultimate gift of life."

Looking ahead

The post-operative period was complicated, but Oswaldo and his family returned home to Oregon in December. "He's steadily improving," said Conrad.

"There are no words to express our gratitude, and we can't say enough about our medical team," said his dad, Martin. "Once we arrived here, we knew we had the best and most experienced care possible."

Added Carmen: "Now, the doctors can use this therapy to treat other patients. Maybe the next family faced with this won't have such a hard decision to make, because it certainly worked for Oswaldo."

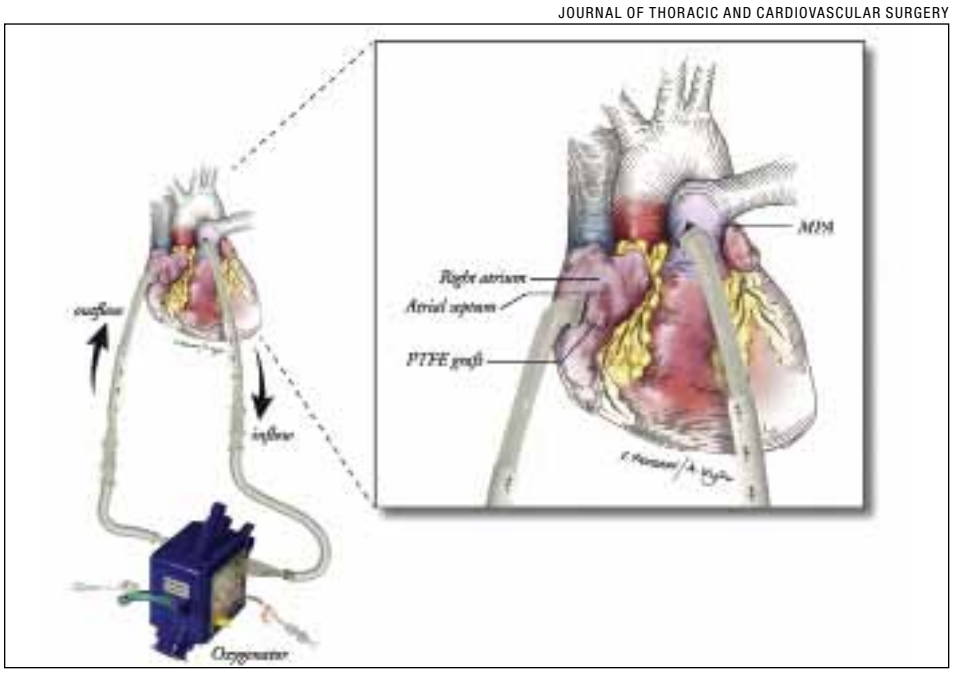
Conrad said the hospital team likely will use this bridge-to-transplant treatment again, adding yet another option to the Stanford Medicine therapies and innovations for kids with failing hearts and lungs.

For Oswaldo, he is simply looking forward to being a kid again. "I want to run and play, and get my life back," he said. As far as what the future holds?

"I just know I want to do something big in life," he said. ISM

Samantha Dorman is media relations manager at Stanford Children's Health.

JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY



SAMANTHA DORMAN

An illustration (top) depicting the bridge-to-transplant system used by Oswaldo Jimenez (bottom, second from right), who is shown here with his family and Carol Conrad, director of the pediatric heart-lung transplant program at Lucile Packard Children's Hospital Stanford.

ss, deliver top-notch care

the white blood cells. Wyatt is one of just 30 infant cases to have ever been reported in the United States. He is at risk of going into anaphylactic shock at any time, and doctors are unsure of the effects an EpiPen — the last line of defense — would have on an infant. The good news: The disease is somewhat manageable with daily medication, a modified lifestyle (limited exercise, heat, cold, sunlight) and frequent check-ups.

"I feel incredibly blessed to live in the Bay Area and have access to this world-class hospital," Shannon said, holding back tears. "They have the expertise that other hospitals don't. If it wasn't for Lucile Packard Children's Hospital we may still not know what was wrong with Wyatt and how to treat him."

Today, Wyatt, who celebrated his first birthday in October, is a perfectly happy boy: He loves to eat avocados, dance to country music, and play with his big brother and big sister. Almost daily they'll meet a stranger concerned that Wyatt has chicken pox or that he's contagious (he's not), and the family takes these opportunities to raise awareness of Wyatt's disease and share his story.

"I love this hospital for a lot of reasons. His doctors are the best," Shannon wrote on a Facebook advocacy page for her son. "They care and each patient truly matters." ISM

Ali Koide is the senior online community manager at the Lucile Packard Foundation for Children's Health.

Weissman

continued from page 1

makes them more money, that's the one they will pursue. There's no one out there looking for who will take the advances of medicine to patients."

Learning how to think

In the early 1950s, Great Falls was the largest city in Montana, with a population around 40,000. It was named for a series of waterfalls on the nearby Missouri River, around which Meriwether Lewis and William Clark portaged in 1805. Low, rolling hills and buttes covered with prairie grasses surround the city, topped by a vast expanse of sky.

In school, Weissman was a good, but not exceptional, student. He struggled with memorization, and didn't particularly enjoy reading. His mother was a classically trained pianist, and Weissman played the piccolo and flute.

When he was about 15 years old, a friend of his mentioned a man named Ernst Eichwald, MD, who had been recruited in 1953 from the University of Utah to work as a pathologist at Montana Deaconess Hospital in Great Falls. Eichwald had made the move on the condition that he be allowed to spend part of his time as a one-man research program, studying the biology of skin transplantation in laboratory mice.

"Instead of working at the scrapyard for my father's hardware store, I went to see Ernst, because my friend said it was fun to be around mice and rats," Weissman said. "But the difficulty was that he was very hard of hearing, and he spoke in a thick German accent. So I couldn't understand anything that he was saying, and I was pretty sure he couldn't understand what I was saying. Finally, in a moment of desperation, I said, 'I'll work for nothing!' Suddenly he understood and could talk to me. So I started to work with him in the summer as mouse caretaker, autopsy assistant and lab researcher."

Weissman continued to work for Eichwald over several summers while he finished high school. During that time, Eichwald carried on his research in mice and chaired the transplantation committee of the National Academy of Sciences. In 1954, he established the Laboratory for Experimental Medicine, which eventually became the McLaughlin Research Institute. He also founded the journal *Transplantation*. From him, Weissman learned not just the fundamentals of scientific research, but also how to think.

KRISTA CONGER

Weissman helps prepare dinner for guests last September at the Montana ranch he co-owns with two friends and fellow scientists.

"Luckily, Ernst never asked me what kind of grades I got in high school," Weissman said. "Because I've never been in the top 10 percent of my class. Not in high school, not in college and not in medical school. I've been successful because of the research papers I wrote. One thing I learned right away from Ernst is that what people teach you from textbooks has very little to do with science. They're trying to teach you the fundamentals, like the periodic table, but not the experiences that lead to an understanding of where that information comes from."

Instead, Eichwald taught Weissman how to puzzle things out for himself. Once Eichwald described the result of an important experiment, but not what the result likely meant to the field of transplantation biology. "I had to guess what was going on, which I did fairly quickly," Weissman said. "I realized from that moment on that I might not be able to memorize the periodic table or chemistry formulas, but I could think."

Conducting experiments

Weissman began to conduct his own experiments in transplantation biology aimed at working out why an adult mouse would reject tissue from a nonmatching donor, but a fetal mouse exposed to blood-forming cells from an adult mouse of a different strain would then accept tissue from that strain of mice for the rest of its life. Work done at that time by Eichwald and Weissman later provided the foundation for organ transplants of all kinds.

As Weissman's scientific career blossomed, he began to mentor younger students in Eichwald's lab. As a high school senior in 1956, he was introduced to Leroy Hood — a fellow Montanan who was then attending his first year at Caltech and is now the director of the Institute for Systems Biology in Seattle. Hood remembers Weissman as a confident researcher who was already conducting seminal experiments in transplantation biology.

"I was a little intimidated by Irv," Hood said. "I hadn't done anything like that yet at all. From day one it was clear that he was going to be a terrific researcher."

Weissman attended Dartmouth for a couple of years but then transferred to what is now Montana State University in Bozeman, where he graduated in 1961. By that time, he had already set his sights on Stanford for medical school because it was a five-year medical program that would allow him time for independent research.

At Stanford, he joined the lab of Len Herzenberg, PhD, and Lee Herzenberg, D.Sc.-equivalent, a husband-wife team of geneticists, before going to work at the end of his first year with Henry Kaplan, MD, a professor of radiology. Kaplan gave Weissman his own lab and a research assistant he shared with Saul Rosenberg, MD, then an assistant professor of radiology.

"It was unusual for a medical student to be given such resources," Rosenberg said. "But I quickly learned that Irv was an extremely bright and experienced researcher. We got to know each other well that year, and I was impressed with his early experience, his dedication and his self-confidence."

Skipping residency

By his junior year, Weissman had recruited other medical students to work with him on researching how the immune system develops to distinguish "self" from "non-self." In 1964 he spent nearly nine months in the laboratory of immunologist Jim Gowans, at Oxford University, where he showed that immune cells that induce tolerance are born in the thymus and then migrate through the blood to the immune-response lymphoid organs like the bone marrow and lymph nodes.

"Once I knew that the thymus was the place that made T cells, and that I could mark them, I decided I wasn't going to do an internship and residency, but was going to do research," Weissman recounted in an oral history done by the American Association of Immunologists in 2013. Kaplan was alone in supporting Weissman's choice. "Everybody, including Saul Rosenberg, got on my case. They said, 'You're never going to be anything if you don't do your internship.'"

"I felt his decision was a mistake," Rosenberg recalled. "He was talented enough to do both clinical and research work. But on the other hand he wouldn't have had the time to dedicate to research that he's had. He chose his path and that has worked out very well for him."

The next two decades saw Weissman doggedly identifying where the many cell types in the immune system were made and how they worked. In 1988, he and his colleagues identified a panel of antibodies that could be used to isolate blood-forming stem cells from mice, a feat that had never before been achieved. Three years later, they did the same with human tissue.

> "It's the people with the common sense to work things out for themselves who will really make a difference in this world."

The purification of these cells suggested the possibility of regenerating tissues, organs and cells damaged by disease or trauma with a person's own stem cells, and eventually set the stage for the formation of the California Institute for Regenerative Medicine, a unique research funding mechanism designed to avoid a repeat of a painful research episode Weissman would experience in the 1990s.

A transformative lesson

The traditional path that promising research findings takes from laboratory to clinic requires the involvement of investors or pharmaceutical companies to finance the expensive clinical trials and commercialization of a new drug or technique. In the late 1980s, Weissman and his colleagues formed a company, SyStemix Inc., to explore the promise of blood-forming stem cells.

At the time, women with advanced metastatic breast cancer were often treated with high-dose chemotherapy in a last-ditch attempt to wipe out tumor cells throughout the body. But this treatment also killed stem cells in the bone marrow, and patients had to be rescued by a transplant of their own stem cells.

Weissman, together with Shizuru and Stanford physicians Karl Blume, MD, and Robert Negrin, MD, realized that the unpurified blood cells traditionally used to reconstitute the immune system often also contained cancer cells. They believed that using purified blood-forming stem cells could avoid disease recurrence, and SyStemix began a clinical trial to test the idea in 1996.

"The idea was that we could use the antibodies identified by Irv to give a patient a tumor-free graft of her own cells," said Negrin, a professor of medicine at Stanford. "The initial results were remarkable. The women who received about 1 milliliter of purified stem cells recovered as quickly and as well as those who received the traditional treatment of several hundred milliliters of unpurified peripheral blood."

COURTESY OF IRVING WEISSMAN

Weissman was a teenager when he first began working with mice in the lab of Ernst Eichwald.

However, a series of pharmaceutical mergers in the late 1990s left the trial, and the rights to the antibodies necessary to isolate pure blood-forming stem cells, in the hands of the pharmaceutical giant Novartis, which abruptly terminated support of the SyStemix stem cell programs in 2000, after the trial completed enrollment in 1998. The decision was likely due, Weissman believes, to the fact that Novartis was at the time pursuing small-molecule drugs like the anticancer medication Gleevec that would give a higher return on their investment than the stem-cell treatment.

"So not only did we not learn the results of the breast cancer trial, we didn't get to continue our planned studies into whether these blood-forming stem cells would allow us to also induce tolerance for transplanted organs like hearts or kidneys. Because they found other drugs that would make them more money, faster. It was simply a business decision.

"So. That was part of my learning."

In a 2011 paper, Weissman and Shizuru reported that five of the 15 women at Stanford who received the purified cells were still living compared to just seven of the 74 who received unpurified peripheral blood.

Through the 'valley of death'

The experience soured Weissman on the involvement of for-profit companies in the translation of research into clinical treatments that could help patients. It also highlighted a phase in medical research known as the "valley of death,"which refers to the fraught time between the identification of a promising finding in a laboratory and when it becomes standard clinical practice, during which money, time and resources are often scarce.

"I realized that this was going to happen again and again and again," Weissman said.

"We were always going to end up taking our research to a certain point and then either venture capitalists or big pharmaceutical companies were going to get it because, unlike universities, they have the funds and the resources necessary to support large clinical trials."

In 2001, President George W. Bush severely re-

See WEISSMAN, page 7

Bacteria

continued from page 1

source for the commensal bacteria that colonize our colons, Sonnenburg said.

Thousands of distinct bacterial species inhabit every healthy individual's large intestine. "We would have difficulty living without them," he said. "They fend off pathogens, train our immune systems and even guide the development of our tissues." While we pick up these microscopic passengers in the course of routine exposures throughout our lifetimes, one of the most significant sources of our intestinal bacterial populations is our immediate family, especially our mothers during childbirth and infancy.

> "There are very few ecosystems where low species diversity is a good thing."

Surveys of humans' gut-dwelling microbes have shown that the diversity of bacterial species inhabiting the intestines of individual members of hunter-gatherer and rural agrarian populations greatly exceeds that of individuals living in modern industrialized societies, Sonnenburg said. In fact, these studies indicate the complete absence, throughout industrialized populations, of numerous bacterial species that are shared among many of the hunter-gatherer and rural agrarian populations surveyed, despite these groups' being dispersed across vast geographic expanses ranging from Africa to South America to Papua New Guinea.

High- versus low-fiber diet

"Numerous factors including widespread antibiotic use, more-frequent cesarean sections and less-frequent breastfeeding have been proposed for why we see this depletion in industrialized populations," said the study's lead author, Erica Sonnenburg, PhD, a senior research scientist at Stanford (she and Justin Sonnenburg are married). "We asked ourselves whether the huge difference in dietary fiber intake between traditional and modern populations could, alone, account for it."

The Stanford researchers employed young laboratory mice that had been specially bred and raised in aseptic environments so that, unlike ordinary mice (and ordinary humans), their intestines were devoid of any microbial inhabitants. After populating the mice's guts with microbes from a human donor, the scientists divided them into two groups. One group was fed a diet rich in plant-derived fiber. The other group's diet, equivalent to the first with respect to protein, fat and calories, was practically devoid of fiber content.

During the experimentation that followed, the researchers analyzed fecal samples from the animals. The two groups' gut-bacteria profiles were initially indistinguishable but soon diverged. "Within a couple of weeks, we saw a massive change," said Justin Sonnenburg. "The low-fiber-intake mice harbored fewer bacterial species in their gut." More than half of these bacterial species' numbers had dwindled by over 75 percent, and many seemed to have disappeared altogether.

After seven weeks, the mice that had consumed a low-fiber diet were switched back to a high-fiber diet for four weeks. Their gut-bacteria profiles partly recovered — probably due to an uptick in abundance of some bacteria whose ranks had declined to undetectable levels during the low-fiber-intake period. Still, this restoration was only partial: One-third of the original species never fully recovered despite their return to a high-fiber diet.

No such changes were seen in the control mice consistently fed a high-fiber diet.

Generational effects

The real surprise came after mice on low-fiber diets had been bred and maintained on low-fiber diets for a few generations. In their experimental confines, these mice were exposed to microbes only through contact with their parents. Each successive generation's gut-bacterial ecosystem declined in diversity. By generation four, the depletion had reached a point where nearly three-quarters of the bacterial species resident in their great-grandparents' guts appeared absent in their own. Even after these mice were put back on a high-fiber diet, more than two-thirds of the bacterial species identified in the guts of their first-generation ancestors proved irretrievable, indicating extinction of those species by the fourth generation of fiber deprivation.

On the other hand, a somewhat more aggressive measure — fecal transplantation — did result in these lost species' retrieval, the study found. Introducing fecal contents of fourth-generation high-fiber-diet mice into the intestines of fourth-generation low-fiber mice, together with putting them on the high-fiber diet for two weeks, fully restored their bacterial profiles. Within 10 days of the procedure, the composition and diversity of the bacteria in the intestines of this group were indistinguishable from those of control mice.

These findings hold major implications for humans, said Erica Sonnenburg. "There are very few ecosystems where low species diversity is a good thing. There's no reason to think our gut is any exception," she said.

Possible fixes

"The extremely low-fiber intake in industrialized countries has occurred relatively recently," noted Justin Sonnenburg. "Is it possible that over the next few generations we'll lose even more species in our gut? And what will the ramifications be for our health?"

Simple tweaks in our cultural practices — for example, not washing our hands after gardening or petting our dogs — could be a step in the right direction, and steering away from overuse of antibiotics certainly is, he said. More extreme measures, such as mass fecal transplants, would require large-scale testing to make sure they are both necessary and safe.

The study was funded by the National Institutes of Health.

Other Stanford authors of the study were graduate student Samuel Smits and life-science research professional Steven Higginbottom.

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

STEVE FISCH

Justin and Erica Sonnenburg and their colleagues found greatly reduced microbial diversity in the guts of mice that had eaten low-fiber diets.

Weissman

continued from page 6

stricted the use of federal funds for human embryonic stem cell research. In response, Weissman and real estate developer Robert Klein, who was associated with the Juvenile Diabetes Research Foundation, worked together to write a proposition to provide $3 billion for stem cell research in California. The proposition passed in 2004.

"We put into that bill, called Proposition 71, that academics could keep doing the research funded by the state agency through the 'valley of death,' through clinical trials," Weissman said.

In the 11 years since Proposition 71 was passed, the National Institutes of Health has initiated four clinical trials using stem cells. In contrast, the state stem cell agency has funded, or supported research that has led to, more than 20 clinic trials to study the ability of the cells combat diseases from skin cancer to blindness to spinal cord injury.

Montana ties

Through the years, Weissman always maintained his ties to Montana. In 1991, he, Hood and Baltimore bought the ranch near Hamilton. Baltimore is a former president of the California Institute of Technology. In 1975 he shared the Nobel Prize in Physiology or Medicine for learning how tumor viruses interact with the DNA of the host cell. Weissman, Hood and Baltimore share time at the ranch, fishing and talking science.

Or at least Baltimore and Weissman fish. In fact, after science, Weissman appears to prefer to talk about fishing above almost anything else.

Hood is another story. "Irv thinks I'm some kind of a mutant," he said. "We've spent many Christmases at the house together, and our families have grown quite close. But I've never enjoyed fly-fishing. What Irv and I do is we enjoy drinks together — drinks, food and talking about science."

Late last year, the McLaughlin Research Institute, founded by Weissman's old mentor Ernst Eichwald, celebrated its 60th anniversary with a symposium featuring Weissman, one of its most notable alumni.

"There's a whole list of alumni of the institute who have done really well scientifically," Hood said, "including five or six like Irv who have made a real impact." Hood and Baltimore serve with Weissman on the institute's scientific advisory board.

Weissman doesn't hesitate to credit the importance of the institute in his early scientific life.

"All of my research can be viewed as a direct result of the lessons I learned 60 years ago from Ernst Eichwald, who let me come into his lab and, instead of telling me what something was, made me think it out for myself; from Jim Gowans, who believed in purifying immune cells to find out what they could do in the body; and from Henry Kaplan, who taught me how to translate discoveries into patient therapies," Weissman said.

Now, Weissman and institute director George Carlson, PhD, along with Klein, have begun discussing the possibility of introducing a bond initiative like Proposition 71 to Montana, on a smaller scale. "This could be one way for researchers in the state to continue to conduct exceptional scientific research, particularly in the area of neurodegenerative and brain diseases, in the face of decreased federal support," Carlson said.

Back at the ranch

On that September evening in his low-ceilinged, well-appointed ranch kitchen, Weissman whipped out an electric carving knife, donned a brown "Montana Trout Unlimited" apron and cut thick slabs of perfectly prepared prime rib to serve the colleagues, lab members and friends shooting pool in the large room next to the kitchen, sipping beer from a local brewery on the patio or wandering in damp and laughing after fishing in the ranch's trout pond.

People discussed their plans for the last, unscheduled days of the Montana trip. There'd be a bluegrass band at the ranch Wednesday. But what to do that weekend?

The buzz of talk subsided briefly as people ate. Then, around a large wooden dining table, Weissman, Shizuru and their lab members went back to doing what they do best: figuring things out. Topics ranged from trouble-shooting experiments and planning future collaborations to how to ensure on the national stage that scientific research remains valued and supported by the public and its leaders.

One thing's for sure: Weissman's never shied away from a challenge. What's more, he feels his unique brand of do-it-yourself problem solving, fostered by Eichwald and Kaplan, applies to all walks of life and every situation.

"Regardless of what career you chose, it's the people with the common sense to work things out for themselves who will really make a difference in this world," Weissman said.

Night fell. People trickled out on foot to their various sleeping quarters while the dark water of the river, full of fishy promise, slid by silently at the edge of the lawn.

A bat or an owl swooped low overhead, and, due to Weissman's persistence, someone, somewhere, was making plans to bake a last-minute birthday cake. ISM

Expert in cancer immunotherapy joins Stanford Medicine faculty

By Erin Digitale

Cancer immunotherapy expert Crystal Mackall, MD, joined the School of Medicine on Jan. 1 as a professor of pediatrics and of medicine, as well as associate director of the Stanford Cancer Institute and co-medical director of the Stanford Laboratory for Cell and Gene Medicine.

As part of her role in the Department of Pediatrics, Mackall is being appointed program leader in pediatric cancer immunotherapy.

Mackall, who previously headed the Immunology Section at the National Cancer Institute in Bethesda, Maryland, and served as chief of the Institute's Pediatric Oncology Branch, will lead Stanford's efforts to advance clinical trials of immune therapies for cancer, with the ultimate goal of moving them to widespread clinical use.

"We are very excited about Crystal's arrival at Stanford," said Hugh O'Brodovich, MD, professor and chair of pediatrics and director of the Child Health Research Institute at Stanford. "She will create an innovative cancer immunotherapy program across Stanford Medicine that will leverage and expand the academic strengths of Stanford University and translate basic science discoveries to treat cancers in children and adults using novel immunotherapy approaches." O'Brodovich is also the Adalyn Jay Physician-in-Chief at Lucile Packard Children's Hospital Stanford, a part of Stanford Children's Health.

Translating discoveries into treatments

As associate director of the Stanford Cancer Institute, Mackall will oversee a multidisciplinary program in cancer immunotherapy. "Cancer immunotherapy is one of the most promising areas in cancer research, showing remarkable results in several previously intractable cancers," said Beverly Mitchell, MD, director of the Stanford Cancer Institute and the George E. Becker Professor in Medicine. "Dr. Mackall is at the forefront of research in this critical area."

"Crystal will be a key player in Stanford's translational research program in stem cell and gene therapy," said Maria Grazia Roncarolo, MD, professor of pediatrics and of medicine and co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine. "Her expertise in the area of engineering T cells to fight cancer is complementary to our existing ability to engineer stem cells and T cells to cure genetic diseases. She also knows how to move fundamental discoveries toward the clinic and toward novel therapies. She's really a fantastic addition to our team."

Mackall is an expert in the field of T cell homeostasis — the maintenance of a healthy number and level of diversity of these immune cells. She has worked at the National Cancer Institute since 1989. After earning a medical degree from the Northeastern Ohio Universities Colleges of Medicine and Pharmacy and completing a residency in pediatrics and internal medicine at Children's Hospital Medical Center of Akron/Akron General Medical Center in Ohio, she moved to the NCI for a fellowship in pediatric hematology/oncology. She advanced through the ranks of NCI investigators, earning the title of tenured principal investigator in 2003 and becoming chief of the pediatric oncology branch in 2008.

Advancing cancer immunotherapy

In addition to her fundamental discoveries in the field of human T cell homeostasis, Mackall's scientific achievements include conducting the first studies in humans of recombinant interleukin-7, a cytokine that can be used in cancer treatment. Her group was one of the first to demonstrate the success of a cancer therapy for pediatric acute lymphoblastic leukemia that works by modifying the patient's own immune cells. The cells are removed from the patient, engineered to express cancer-specific receptors and returned to the patient, where they attack the cancer.

Mackall also serves as co-leader of Stand Up 2 Cancer's Pediatric Cancer Dream Team, a multi-institutional program focused on developing novel immunotherapies for childhood cancer. She holds patents or has patents pending for nine advances in cancer immune therapy.

"We have entered the golden age of immunotherapy for cancer," Mackall said. "I think Stanford's depth of scientific excellence and innovation will play a fundamental role in advancing this field. I'm excited to have the chance to develop a vibrant translational research program focused on cellular therapy for cancer, building upon all of the university's existing strengths."

Mackall's recruitment is in line with Stanford's strategic decision to invest in research that aims to translate scientific discoveries into clinical treatments for several categories of previously intractable disease, including a number of genetic diseases and cancers, Roncarolo said.

Mackall joins experts in genetic diseases, tissue-specific diseases and complex diseases that could potentially be treated with stem cell, gene therapy and immunotherapy techniques. To help the team implement these novel technologies, Stanford will open the Laboratory for Cell and Gene Medicine this year, a Good Manufacturing Practice compliant facility.

"This program puts Stanford in a unique position to be a world leader in stem cell and gene therapies and regenerative medicine," Roncarolo said. **ISM**

NORBERT VON DER GROEBEN

Crystal Mackall will lead Stanford's efforts to advance clinical trials of immune therapies for cancer.

Faculty members appointed to endowed professorships

Six Stanford Medicine faculty members have been appointed to endowed professorships.

STEVEN ARTANDI, MD, PhD, professor of medicine and of biochemistry, was appointed the Jerome and Daisy Low Gilbert Professor, effective Dec. 8. His research focuses on the underlying causes of cancer and degenerative diseases, and new therapies to treat those conditions.

This professorship was established to support a faculty member who conducts basic science research that benefits humanity, with a focus on researchers using stem cells or regenerative medicine.

LINDA BOXER, MD, PhD, vice dean of the School of Medicine, chief of hematology and professor of medicine, was appointed the Stanley McCormick Memorial Professor, effective Oct. 6. Her research focuses on the molecular mechanisms of oncogene deregulation.

This professorship is intended to encourage and support women who are studying medicine, teaching medicine or conducting medical research. It was established with assets from a bequest given in 1969 by the late Katharine McCormick to honor her husband, Stanley.

ANNE BRUNET, PhD, professor of genetics, was appointed the Michele and Timothy Barakett Endowed Professor, effective Dec. 8. Her research focuses on the genetic mechanisms of aging and longevity.

This professorship was created by Michele and Timothy Barakett to support work on computational biology, inflammation, immunology and allergies, with a focus on improving child health.

THOMAS CLANDININ, PhD, professor of neurobiology, was appointed the Shooter Family Professor, effective Dec. 8. His research focuses on the development and functioning of nerve-cell circuits.

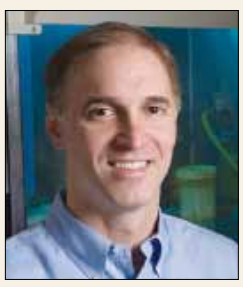
This professorship was created to support a faculty member in the Stanford Neurosciences Institute. It was established in January 2014 with gifts from Eric and Elaine Shooter. Eric Shooter, PhD, is a professor emeritus of neurobiology.

LEONORE HERZENBERG, D.Sc.-equivalent, was named the Department of Genetics Flow Cytometry Professor, effective April 14, 2015. Her research focuses on gene regulation in the immune system, development and function of B cells, and the development of automated software for analyzing research and clinical flow cytometry data collected with the fluorescence-activated cell sorter, or FACS.

This professorship was established to honor the contributions of the late Leonard Herzenberg, PhD, and his wife, Leonore, who together developed the first FACS, an instrumental tool in immunology, stem cell research and proteomics. The funds came from a variety of sources, including friends and former students of the Herzenbergs.

JOSEPH WU, MD, PhD, director of the Stanford Cardiovascular Institute and professor of medicine and of radiology, was appointed the Simon H. Stertzer, MD, Professor, effective Oct. 6. His research focuses on cardiovascular stem cell biology, genomics and imaging.

This professorship was created in 1998 to encourage innovation in interventional cardiology and develop treatments for vascular disease. It was established by Simon H. Stertzer, MD, professor emeritus of medicine. **ISM**



Steven Artandi

Linda Boxer

Anne Brunet

Thomas Clandinin

Leonore Herzenberg

Joseph Wu