INSIDE STANFORD MEDICINE

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A new study links common male medical condition to vascular disease.

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New children's hospital opens its doors

By Kate DeTrempe

BETH BARTON / DNK DIGITAL

A ribbon-cutting ceremony was held Nov. 30 at Lucile Packard Children's Hospital Stanford to celebrate the completion of the hospital's new main building.

When Diane Flynn's third child was born with a cleft lip in 2001, her family embarked on a series of six surgeries and appointments with dozens of specialists at Lucile Packard Children's Hospital Stanford that spanned eight years. For the Flynns, the hospital became a second home.

It wasn't long before Flynn felt compelled to give back to the hospital that was so supportive of her family, so she contacted the director of the hospital's Family Advisory Council and became one of five parent leaders of the group, which provides firsthand feedback on everything from bedside care to food service.

Eight years later, in 2009, the hospital team that was starting to plan for a new children's facility wanted to gain an understanding of needs from the perspectives of a wider group. They created a design committee that included representatives from the project's two architectural firms, hospital staff, board members, faculty and members of the Family Advisory Council.

"About 10 years ago, before the design team or architects had plans, they had parents," said Flynn, who joined the committee as her son, Matthew, now 16, was spending less time in treatment. She wanted to be a voice for families like hers.

The committee's meetings became open forums for input and brainstorming about what they wanted to see in the new campus. "It didn't take long for us all to agree — a restorative space that felt light, healing, engaging," Flynn said.

That feedback about the ambiance and surroundings in the new space is present in nearly every aspect of the new building, which opened Dec. 9. The building, which houses the medical community's most advanced medical tools, is meant to be responsive to changes in pediatric care as it evolves.

But the guiding principle for the facility is to reflect a holistic approach to healing — focusing on the family at the heart of patient care and creating a restorative environment by integrating nature and art. The concept is reminiscent of Lucile Salter Packard's founding vision for the hospital: to nurture the body and soul of every child. She recognized the power of nature as an important part of healing. She wanted kids to be treated like kids — not just patients. And she believed that caring for a child involved the whole family.

Feelings matter

There is deep evidence that a hospital's physical environment and the well-being of patients and families are closely related. In 1984, two years before planning for the existing Packard Children's Hospital began, *Science* published a study by environmental psychologist Roger Ulrich, PhD, that was lauded as the first to use modern medical research to support the healing effects of nature, an approach he called "evidence-based design." Ulrich studied 23 gallbladder surgery patients who recovered in rooms with windows looking into a natural scene and 23 whose rooms looked out to a brick wall. He found that the patients with views of nature stayed in the hospital an average of one less day, had 3.5 times fewer negative comments from nurses, such as "frustrated

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Gut bacteria produce druglike molecules that can affect intestinal, immune health

By Sarah C.P. Williams

Here's some food for thought: When you licked your Thanksgiving plate clean, you weren't just feeding yourself; you were also providing meals to the trillions of microbes that live in your gut.

And if your dinner included turkey, a notoriously rich source of the amino acid tryptophan, the gut bacterium *Clostridium sporogenes* would have had the job of breaking down that tryptophan. Then the molecules produced by the microbe would have flowed into your bloodstream in the same way a prescription drug might, interacting with your immune system and changing the biology of the intestines.

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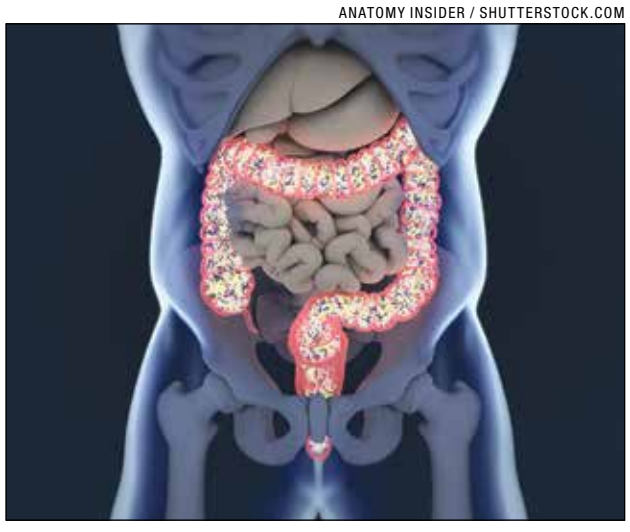

Researchers have shown that the composition of a person's gut microbiome can alter their risk for all sorts of health problems.

School of Medicine researchers have used mice to demonstrate how gut bugs could be bioengineered to produce possibly therapeutic changes in the body.

A paper describing their efforts was published online Nov. 22 in *Nature*. Justin Sonnenburg, PhD, associate professor of microbiology and immunology, and Michael Fischbach, PhD, associate professor of bioengineering, share senior authorship. The lead author is Dylan Dodd, MD, PhD, instructor in pathology.

When the researchers blocked the ability of *C. sporogenes* to break down tryptophan in mice, levels of certain molecules in their bloodstreams changed. Moreover, the researchers saw physiological changes to the mice's immune systems and intestines.

"This is a vivid example of not only how the microbiome is affecting things all over your body, but of how we can leverage that to improve health," said Sonnenburg, using a term for the collection of microbes living on or inside an animal, or in a particular part.

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Clinical trial points to potential cell therapy for relapsed leukemia

By Krista Conger

A significant proportion of children and young adults with treatment-resistant B-cell leukemia who participated in a small study achieved remission with the help of a new form of gene therapy, according by researchers at the School of Medicine and the National Cancer Institute.

Crystal Mackall

The therapy is similar to but distinct from CD19-targeted chimeric antigen receptor T-cell therapy, or CAR T-cell therapy, in which a patient's T cells are genetically modified to target a molecule called CD19 on the surface of the cancer cells. This therapy was recently approved by the Food and Drug Administration for the treatment of some types of blood cancers.

The new therapy genetically modifies a patient's T cells to target a different molecule called CD22. The new approach is helpful because the cancer cells of some patients who undergo CD19-directed CAR T-cell therapy stop expressing the CD19 molecule on the cell surface.

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Study: Stem cells that generate fat tissue have circadian clock

By Erin Digitale

A circadian clock is embedded in the stem cells that give rise to fat and plays a decisive role in determining when the cells mature, according to a new study by researchers at the School of Medicine.

The study, which was published online Nov. 28 in *Cell Reports*, shows that adipocyte precursor cells, as these stem cells are called, have a circadian clock that functions differently than the kind found in most of the body's other cells. Perturbing the clock changes the pace at which the cells turn into mature adipocytes, or fat cells. The discoveries could help explain why night-shift workers are at risk for metabolic diseases, such as diabetes.

"Before this study, we knew we could disturb someone's circadian clock and change their metabolism, but how that happened at a cellular and molecular level was very mysterious," said Brian Feldman, MD, PhD, senior author of the study and assistant professor of pediatrics at Stanford. Postdoctoral scholar Abhishek Agarwal, PhD, and research assistant Maria José Costa PhD, share lead authorship.

NORBERT VON DER GROEBEN

Brian Feldman is the senior author of a study that may help explain why shift workers are prone to metabolic diseases, such as diabetes. The study's findings were published online Nov. 28.

Prior research had shown that mature fat cells have a circadian clock, but it was not known if a clock existed in their stem cells. The role of the clock in helping the cells decide when to mature was a surprise to the researchers.

A specific protein, a cog in the workings of the clock, drives the cells' differentiation process, Feldman's team found. "We think this mechanism prevents you from making adipocytes when you don't need to," he said.

Integrating hormone signals

Several hormonal signals that influence fat maturation are known to rise and fall in patterns throughout the day. Glucocorticoids, such as the stress hormone cortisol, are typically highest just before waking. Insulin rises in response to meals. In a lab dish, adipocyte precursor cells can be induced to mature by adding large doses of glucocorticoids or insulin, but the cells do not mature every time the body experiences surges of these hormones in real life.

"The cells do not just take any one signal as 'go or no go' to differentiate," Feldman said. "Embedding a clock in the differentiation pathway integrates all the signals. They all have to be in alignment before the cells push forward."

In most cell types, the core circadian clock machinery consists of a family of proteins, whose levels oscillate over the course of the day, encoded by three genes: Per1, Per2 and Per3.

To look for a circadian clock in adipocyte precursor cells, Feldman's team needed to track the cells in living mice. They developed several strains of genetically modified mice for their experiments.

First, they used mice whose cells express luciferase, a fluorescent protein, whenever the Per2 gene is expressed, which they used to show that the adipocyte precursor cells do have a circadian clock; the cells exhibit daily oscillations in Per2 expression.

The team then studied what happened over a full day to expression of the three Per genes in mice that were kept in constant darkness. Keeping the animals in darkness enables researchers to separate intrinsic functions of the circadian clock from those that occur in response to external dark-light cycles.

To their surprise, the researchers saw that Per1, a core component of the circadian clock in most cell types, does not oscillate in adipocyte precursor cells. However, expression of both the Per2 and Per3 genes oscillates in a daily rhythm. The oscillations of Per3 were intriguing because the gene previously had been considered unimportant, as mice lacking Per3 show no major changes in their sleep-wake patterns.

But follow-up experiments by Feldman's team demonstrated that Per3 plays a big role in adipocyte precursor cells. Mice lacking the Per3 gene had higher levels of fat-cell maturation than those with a functioning Per3 gene, and mice that overexpressed Per3 blocked fat cell maturation. The Per3 protein acts directly with another protein to regulate a gene known to begin the cells' maturation process, the researchers found.

Effects of shift work

Extensive research has shown that late-shift workers, who are awake at night and asleep during the day, are at increased risk for diabetes and obesity. But scientists have not known why.

"This work is connecting the dots of how altered biological rhythms can lead to metabolic derangement," Feldman said. In those who sleep at night, the adipocyte precursor cells' circadian clock guards against maturing too many fat cells. "But what happens in shift workers is that this ends up working against you," he said. "If the rhythm of making mature adipocytes is thrown off and you're not making adipocytes when you should, that may place you at greater risk for diabetes in the future."

Future research may address how the discovery could help prevent metabolic disease, Feldman said, though he cautioned that using the new discovery to prevent fat cells from maturing would not necessarily be desirable. Extra fat from the diet will go to other tissues if it cannot be stored in fat cells, and excess fat in locations such as the liver or muscle can be damaging.

The new research also illuminates a long-debated question: Should we avoid snacking at night?

"I have to say, I think there's some truth to that," Feldman said. "I do think the timing of our meals is an overlooked factor; our bodies work best if we eat in defined periods during the day, and not during periods when we are not supposed to be active."

The study's other Stanford authors are postdoctoral scholars Belén Rivero-Gutiérrez, PhD, and Lijuan Ji, PhD; and graduate student Stefanie Morgan.

The research was funded by the National Institutes of Health, Stanford's SPARK Translational Research Program, the Lucile Packard Foundation for Children's Health and the Stanford Child Health Research Institute.

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

Drug for spinal muscular atrophy prompts ethical dilemmas

By Patricia Hannon

When the Food and Drug Administration approved the first drug for people with spinal muscular atrophy a year ago, clinicians finally had hope for improving the lives of patients with the rare debilitating muscular disease. But the extraordinary cost of the drug and complicated logistics of delivering it present barriers for many patients, according to experts in bioethics at the School of Medicine.

They teamed up with colleagues at several other institutions to discuss concerns related to the medication in an article that was published Dec. 11 in *JAMA Pediatrics*.

Chief among those concerns is that the $125,000-per-dose cost of the drug, nusinersen, could restrict long-term patient access to it and the ability of clinics to provide it.

"I don't think anyone looks at the evidence that we've seen so far and thinks that it's a bad idea to use the medication as an option for patients. But the cost really ends up being a significantly limiting factor," said Alyssa Burgart, MD, MA, medical director of clinical ethics at Lucile Packard Children's Hospital Stanford and assistant professor of anesthesiology, perioperative and pain medicine at the university.

Other concerns, she said, include the lack of guidelines about fair allocation of the drug, uncertainty about its lasting benefits and the risks of treatment.

Burgart is the article's lead author. Chris Feudtner, MD, PhD, of the University of Pennsylvania and Children's Hospital of Philadelphia, is the senior author.

'A huge step'

Burgart said it's an exciting time for treating spinal muscular atrophy, or SMA, and that the drug is a "game-changer" for families. "It's not a cure," she said. "But it's a huge step, and you hate for the price tag to be the reason that a family has to be devastated all over again, as if the devastation of a diagnosis isn't enough."

Spinal muscular atrophy is a rare genetic disease that interferes with the body's ability to make the survival motor neuron protein, without which patients lose muscle control and strength, and eventually the ability to move, swallow or breathe. The most common type of the disease is SMA-1, which is diagnosed in babies between birth and 6 months old.

Nusinersen, which is injected into the spine and works by temporarily enabling SMA patients to make more of the survival motor neuron protein, is one of the most expensive drugs on the market. Six injections are required in the first year, at a cost of $750,000, and three are required in subsequent years, at a cost of $375,000 a year. Insurance companies cover some patients, but the criteria aren't uniform. It's also unclear how long insurance companies will cover a particular patient.

Burgart said clinicians have encountered cases in which insurance companies cover the medication only for the younger of two siblings because the older child has more disabilities so doesn't meet their criteria for covering the progressive disorder. "I don't know what it's like to be that parent and to have the joy at the opportunity to potentially modify one child's life, and not have the opportunity for your slightly older child. It's a very cruel time, I think," she said.

Before the FDA approved nusinersen, which is marketed by Biogen and Ionis Pharmaceuticals as Spinraza, the only care options were palliative care or supportive care, including physical therapy, respiratory help or assistive devices. Most babies diagnosed **See ETHICAL, page 3**

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STANFORD MEDICINE

Researchers discover second 'don't eat me' signal on cancer cells

By Krista Conger

NORBERT VON DER GROEBEN

Irving Weissman and his collaborators have found a second pathway that could be used in efforts to boost the body's ability to kill cancer cells. Their study appeared online Nov. 27 in *Nature Immunology*.

A second biological pathway that signals immune cells not to engulf and kill cancer cells has been identified by researchers at the School of Medicine.

An antibody that blocks the "don't eat me" signal has shown promise as a cancer treatment in animal models and is currently in clinical trials. Combining that antibody, known as anti-CD47, with another that blocks this newly discovered pathway could further enhance the ability of the immune system to eradicate many types of cancers, the researchers believe.

"The development of cancer cells triggers the generation of SOS molecules recognized by the body's scavenger cells, called macrophages," said Irving Weissman, MD, the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, and also of its Ludwig Cancer Center. "However, aggressive cancers express a 'don't eat me' signal in the form of CD47 on their surfaces. Now we've identified a second 'don't eat me' signal and its complementary receptor on macrophages. We've also shown that we can overcome this signal with specific antibodies and restore the ability of macrophages to kill the cancer cells."

A paper describing the findings was published online Nov. 27 in *Nature Immunology*. Weissman, a professor of pathology and of developmental biology, shares senior authorship of the study with former postdoctoral scholar Roy Maute, PhD, who is now head of biology at Ab Initio Biotherapeutics Inc. Graduate student Amira Barkal shares lead authorship with former graduate student Kipp Weiskopf, MD, PhD, who is now a resident at Brigham and Women's Hospital.

"Simultaneously blocking both these pathways in mice resulted in the infiltration of the tumor with many types of immune cells and significantly promoted tumor clearance, resulting in smaller tumors overall," Barkal said. "We are excited about the possibility of a double- or perhaps even triple-pronged therapy in humans in which we combine multiple blockades to cancer growth."

> "We are excited about the possibility of a double- or perhaps even triple-pronged therapy."

Importance of macrophages

Macrophages are large white blood cells found in nearly all the body's tissues. As part of what's known as the innate immune system, they engulf and kill foreign invaders like bacteria or viruses. They also destroy dead and dying cells and, in some cases, cancer cells whose internal development cues have gone haywire.

The "don't eat me" signal was identified in Weissman's laboratory in 2009. His team found that nearly all cancer cells express high levels of a molecule called CD47 on their surfaces. They showed that CD47 binds to a protein called SIRPalpha on the surface of macrophages, inhibiting their ability to kill the cancer cells.

Animal studies showed that treatment with an anti-CD47 antibody vastly improved the ability of macrophages to kill cancer cells and even led to some cures in mouse models of cancer. Phase-1 clinical trials are currently underway at Stanford and in the United Kingdom to test the safety and efficacy of the treatment in humans with a variety of blood and solid tumors.

Component of adaptive immunity

The newly discovered binding interaction used by cancer cells to evade macrophages capitalizes on a protein structure on the cancer cells' surface called the major histocompatibility complex class 1, or MHC class 1. Human tumors that have high levels of MHC class 1 on their surfaces are more resistant to anti-CD47 treatment than are those with lower levels of the complex, the researchers found.

MHC class 1 is an important component of adaptive immunity, the second major arm of the immune system, which relies on immune cells called T cells and B cells to nimbly and specifically respond to foreign invaders and cell damage. Most cells of the body express MHC class 1 on their surfaces as a way to indiscriminately display bits of many proteins found within the cell — a kind of random sampling of a cell's innards that provides a window into its health and function. If the protein bits, called peptides, displayed by the MHC are abnormal, a T cell destroys the cell. Although the relationship between MHC class 1 and T cells has been well-established, it's been unclear whether and how the complex interacts with macrophages.

Barkal and her colleagues found that a protein called LILRB1 on the surface of macrophages binds to a portion of MHC class 1 on cancer cells that is widely shared across individuals. This binding inhibits the ability of macrophages to engulf and kill the cancer cells, both when growing in a laboratory dish and in mice with human tumors, the researchers found. Inhibiting both the CD47-mediated pathway and the LILRB1 pathway significantly slowed tumor growth in mice.

Understanding the balance between adaptive and innate immunity is important in cancer immunotherapy. For example, it's not uncommon for human cancer cells to reduce the levels of MHC class 1 on their surfaces to escape destruction by T cells. People with these types of tumors may be poor candidates for cancer immunotherapies meant to stimulate T cell activity against the cancer. But these cells may then be particularly vulnerable to anti-CD47 treatment, the researchers believe. Conversely, cancer cells with robust MHC class 1 on their surfaces may be less susceptible to anti-CD47.

"In some cancers, MHC class 1 expression, for a variety of reasons, is not reduced," Weissman said, "and this helps the cancer cells escape from macrophages. These findings help us understand the many ways cancer cells can evade macrophages, and how we might block these escape pathways."

"The fact that there are at least two redundant mechanisms to modulate macrophage activity is a testament to how critically important it is to tightly control our immune responses," Barkal said. "It's possible that future studies will identify even more of these pathways, which will give us additional targets for cancer immunotherapy."

The research was supported by the National Institutes of Health, the D.K. Ludwig Fund for Cancer Research, the Cancer Research Institute, the Human Frontier Science Program Organization, the University of Wisconsin Medical Scientists Training Program, the National Research Award, the Paul and Daisy Soros Fellowship for New Americans, the Stanford Medical Scientist Training Program and anonymous donors.

Other Stanford authors are technician Kevin Kao; former graduate student Sydney Gordon, PhD; postdoctoral scholar Benyamin Rosental, PhD; graduate students Ying Yiu, Benson George, Jonathan Tsai and James Chen; research associate Maxim Markovic; former medical fellow Nan Ring, MD; former research assistants Kelly McKenna and Po Yi Ho; and former undergraduate student Robin Cheng.

Weissman, Maute and Weiskopf are co-inventors on a patent related to the current work and own stock in Forty-Seven Inc., which is pursuing clinical approval of the anti-CD47 antibody. Weissman, Maute, Weiskopf and James Chen are stockholders or consultants or employees of the company.

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

Ethical

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with SMA-1 die before their second birthday, but patients with SMA types that show up later in life live longer.

Early treatment crucial

Early treatment of SMA is crucial for halting muscle degeneration, especially in infants, Burgart said. A blind national clinical trial of nusinersen involving 121 SMA-1 patients found that babies receiving the drug showed significant motor function improvement when compared with babies in the trial who didn't get the drug. The results were significant enough to prompt the FDA to halt the trial early, in August 2016, and expand access to all SMA-1 patients. But early approval left medical centers scrambling to establish treatment programs, which became more urgent when the FDA approved the drug for all SMA patients in December 2016, Burgart said.

Even before final FDA approval, neuromuscular and biomedical ethics teams at Stanford, including pediatric neurologist and SMA expert John Day, MD, PhD, were already collaborating with colleagues around the country to grapple with the practical and ethical challenges of providing treatment.

"It really was thinking about ethical issues as they were coming up: 'How can we provide frameworks for what the issues are — and what are the fair and ethical ways to address them?'" said one of the article's co-authors, Holly Tabor, PhD, associate professor of medicine at Stanford and assistant director of the Stanford Center for Biomedical Ethics.

For example, what would be required to set up SMA treatment programs with high standards of care? How many patients could each clinic accept? How many programs were needed? How would clinics manage waiting lists? Would they have benchmarks, such as disease progression levels, for deciding who gets treatment? Is patient improvement the only measure of success, or is it also maintaining **See ETHICAL, page 6**

Stanford Medicine to collaborate on Apple Heart Study

Stanford Medicine researchers are working with Apple on a research study to determine whether the Apple Watch's heart-rate sensor can identify irregular heart rhythms associated with a condition known as atrial fibrillation.

The Apple Heart Study app was launched Nov. 30. As part of the study, if an irregular heart rhythm is observed, participants will receive a notification on their Apple Watch and iPhone, a free consultation with a study doctor and an electrocardiograph patch for additional monitoring.

Each year in the United States, atrial fibrillation causes 130,000 deaths and 750,000 hospitalizations. It can lead to blood clots and is a leading cause of stroke, but many don't experience symptoms, so it often goes undiagnosed.

The sensor in the Apple Watch uses LED lights to measure heart rate. The technology can also monitor the pattern of the heartbeat. The app uses this technology combined with software algorithms to identify an irregular heart rhythm.

"Through the Apple Heart Study, Stanford Medicine faculty will explore how technology like Apple Watch's heart-rate sensor can help usher in a new era of proactive health care central to our precision health approach," said Lloyd Minor, MD, dean of the School of Medicine.

Doctors and medical researchers around the world have been using iPhone and Apple Watch to study various aspects of health. To date, Apple's ResearchKit and CareKit platforms have been used by over 500 researchers and more than 3 million participants. **ISM**

Packard

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behavior" or "upset and crying," and took fewer and weaker medications compared with the other patients.

"By the early 1980s, evidence supporting the stress-reducing effects of nature was so consistent, and we understood that natural beauty's effects were much more than skin deep," Ulrich said. "I began to wonder where could this be useful, and the main answer surfaced at hospitals — a location where people are captive for a period of time if they're bedridden, where they are experiencing stress and pain, and for whom distraction facilitated by looking at nature might help improve recovery outcomes."

Now, he explained, it is routine for hospitals to be built to support a positive psychological experience for patients, but he points to the existing Packard Children's Hospital as "an early adopter" when it opened in 1991.

"It was one of the first hospitals I was consciously aware of that had explicitly used the emerging field of evidence-based design to inform the design," he said of the facility, which was acclaimed for having nature-based and family-centered themes, with terraces on each floor and a garden at the center.

Architects of the new building, which is connected to the existing hospital, took a similar approach by challenging the fundamental mindset of being inside a hospital, beginning with the experience of patients as they arrive.

"A common issue in health care is that traditional hospital design places operating rooms and imaging services on sub-ground-level floors to accommodate heavy surgical and diagnostic equipment," said Robin Guenther of Perkins+Will, lead architect for the new building. Perkins+Will collaborated with HGA on the project. "In the last generation of hospital building about 30 years ago, people weren't really crafting an experiential journey for patients. They were focused on accommodating the technology — hospitals for machines."

"From a patient experience perspective, it is revolutionary."

But the practice of moving patients down into a basement level, she explains, can exacerbate feelings of fear or anxiety that patients — particularly children — experience prior to such "scary procedures" as surgery. Reflecting a shift away from this, the new hospital's pedestrian entrance is at ground level, which is also the location of the treatment center (surgery, interventional services, imaging and nuclear medicine). Families don't have to traverse below ground and instead enter the main lobby and have only a few choices about where to go next: up the staircase or elevator, or across the lobby into the surgery and imaging unit.

"From a patient experience perspective, it is revolutionary," Guenther said.

The challenge is that the most public part of the new hospital — the lobby — is directly adjacent to the most private area — the surgical treatment center. To marry these spaces, lobby walls are lined with enclosed alcoves where families can wait. On each ascending inpatient floor, open spaces contain wood-paneled niches that resemble treehouses to provide private spaces for those who seek it.

"What we heard from families is that when they aren't in a patient's room, they tend to gather in public spaces, rather than in waiting rooms behind closed doors," explained Jill Sullivan, vice president of strategic space planning and general services.

Architects also wanted to reflect elements of Northern California's native environment to provide a sense of being alongside nature as you move through the building, despite being in a hospital, Guenther said.

Outside, 3 ½ acres of gardens and green space surround the building, and inside, waiting areas have large picture windows. Each patient room has a planter box outside the window and a view to the gardens, and about 150 feet of the new cafeteria space is lined with glass doors that open to an outdoor dining patio overlooking a garden. The garden has native plants and animal installations that represent California's eco-regions, including a puma den, a gopher's burrow and a redwood tree fort.

BETH BARTON / DNK DIGITAL

(Right) Stanford Medicine cardiologist Gail Wright with one of her patients, Tyler Briend, in the hospital's new main building. (Bottom) The exterior of the new building.

Most uniquely, each of the building's four patient care levels has two outdoor decks — one for patients and visitors, and one for staff.

"Patients, family members, visitors, even staff can be too pressed for time to travel down the elevator and search outside for a garden," Ulrich said. "To have a restorative, outdoor area on each floor is very important from the standpoint of ensuring easy access to nature and thus positively impacting patient health."

Guenther said that, in the past, safety concerns prevented the construction of outdoor spaces on above-ground levels.

"The idea of outdoor space on nursing units is one where Packard Children's is at the beginning of a new curve in design," she said, explaining that 6-foot-tall tempered safety glass panels enclose each deck to prevent people from falling. "It is a new generation of outdoor space that really is easily accessible to patients and families."

The hospital's use of natural light and focus on a holistic approach to healing is also embodied in the sanctuary space, which includes a private healing garden and access to a meditative labyrinth. The concept breaks a mold that was popularized during the increased secularization of health care beginning in the latter half of the 20th century, when design shifted from common cathedral-inspired hospital chapels to minimalistic spaces.

BETH BARTON / DNK DIGITAL

Will Bolick, a patient at the hospital, attended the ceremony.

"In the last generation of hospitals, the idea of spiritual space became so minimal that it became a conference room. This hospital reintroduces a sanctuary space that is truly special," Guenther said.

As the new sanctuary was conceptualized, the team again called on the Family Advisory Council, whose members represent a variety of faiths (and nonfaith), to build something that would appeal to many spiritual beliefs and backgrounds. The result "is a space that is multicultural, multidimensional and goes beyond religious practice," Guenther said. "It is about recognizing that we are whole people who have physical bodies, minds and a spirit and we need to provide a place for people to keep in touch with that."

Sweating the small stuff

For patient rooms, architects took care to treat them as the center of a child's hospital experience, and not just a place for essential medical equipment and visits from clinicians.

Architects designed them to be healing, comfortable spaces for the whole family. Nearly all of them are private and more spacious to serve as home base for mealtimes, movies and games and include sleeping accommodations for two family members.

"When a parent can have a private room, their own space with their child, they can create a quiet and healing space," said Karen Wayman, director of the Family Advisory Council. "That's so important for a parent's relationship with their child."

To refine the rooms, full-scale detailed mockups were constructed in an off-site warehouse. Everything was in place, including medical equipment, patient beds, sinks, televisions, light switches, outlets and hand sanitizer dispensers. Then representatives from the full care team of physicians, nurses and parents walked through to share feedback.

"We reviewed bedside tables, tried different sleeper beds, tested the comfort of rocking chairs, examined the distance from the couch to the patient's bed, to the television and to the phone charger built into the wall," Flynn said. "Everyone had a different perspective. For me, the lighting was really important. When my son was in the hospital, I didn't want to disturb him by turning on the overhead lighting to read, so for the new building the design committee made sure we would have cozy reading lights in each room."

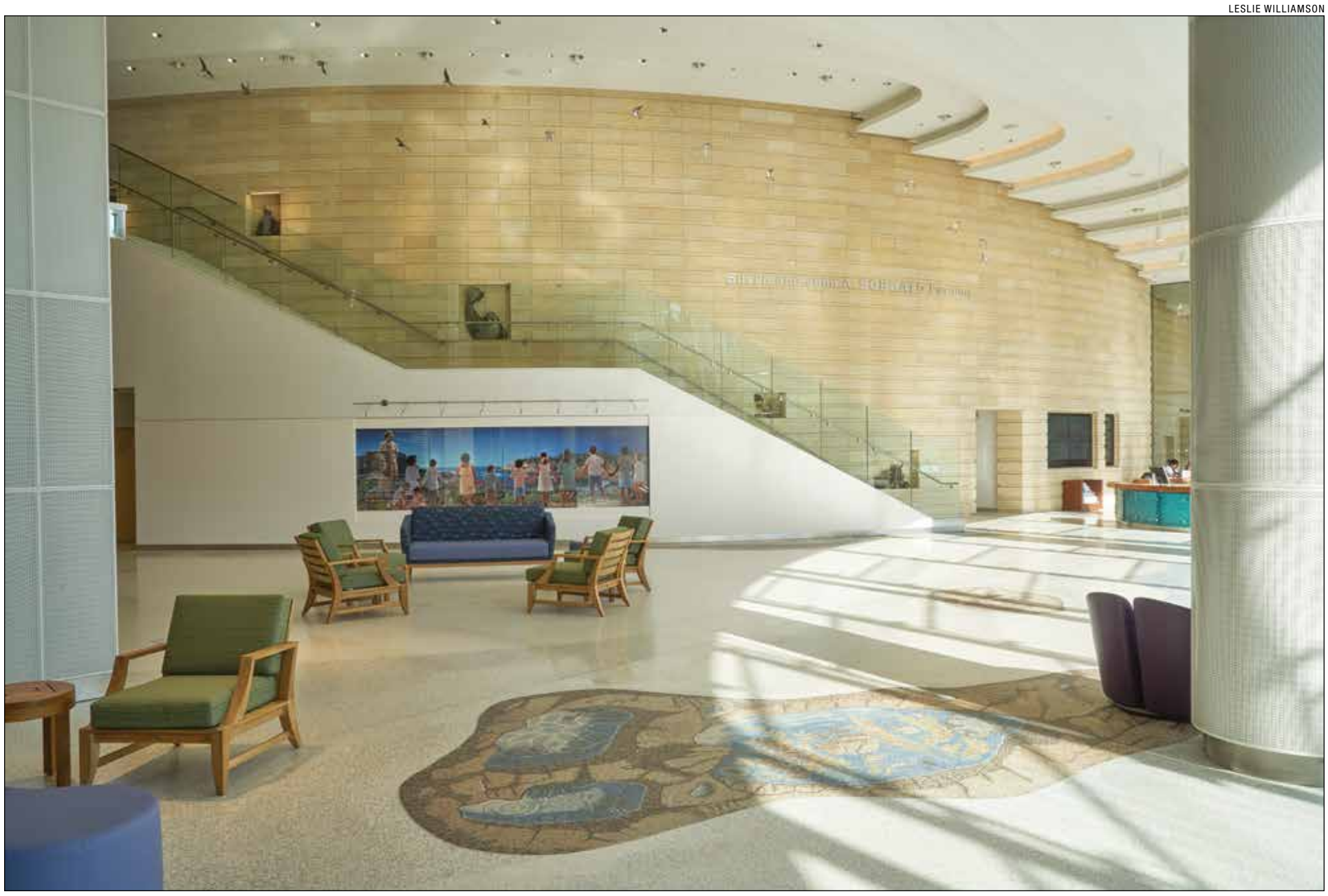
Parents also championed having bathtubs in many of the bathrooms instead of standing showers to make bath time easier for little ones. Their input also resulted in the inclusion of a family lounge, laundry facilities and family kitchen on every patient floor to help families maintain day-to-day routines. "You just don't think about it until you walk it from a patient or parent perspective," Flynn said.

The collaboration between providers and parents was key, Wayman explained. "Providers learned about the parents' experiences in the hospital, and parents had an opportunity to see how things worked from the provider prospective," she said.

"Both sides of the equation were critical to creating a healing space."

Physicians, nurses and other health care team members evaluated where equipment would be placed and

LESLIE WILLIAMSON



BETH BARTON / DNK DIGITAL

(Top) The lobby of the new hospital building. (Bottom) Harry Watson and his sister Effy Watson, a former cancer patient at Packard Children's, in the hospital's Dunlevie Garden.

whether there was enough room to maneuver when treating children in their rooms, and weighed in on aesthetic details. When pediatric anesthesiologist Chandra Ramamoorthy, MD, saw that the rooms were painted periwinkle blue and yellow, she instantly knew they would need to be changed. In the blue rooms, it would be difficult to ascertain between the reflection of the wall color and cyanosis — a bluish discoloration in patients whose blood isn't getting enough oxygen.

"We had initial designs in place for the room mockups, and I don't think a single thing stayed the same," Sullivan said. "Every design choice for the new building was made with the intent to put autonomy and control into the hands of children and families, staff and providers, and frankly we wouldn't have thought about these details without engaging the staff and the families who will actually be using the space."

Stimulating the mind, restoring the body

Finally, priority was placed on families being able to connect the worlds of learning and healing, mind and body, resulting in a space that includes abundant access to nature, art installations, play spaces and other interactive elements.

"You're always trying to engage your child in something when you're in the hospital. When my son had to fast before his surgeries, we would walk the halls to try to keep his mind off his hunger," Flynn said. "We'd stop at the art on the walls and play 'can you find' games. Bringing in art and other elements of interactive play like this to the new hospital was crucial."

Thematically, opportunities to learn about the local environment and nature themes are prominent across the campus. Paths of animal footprints native to California are implanted throughout the hospital's gardens for visitors to follow and learn about the state's diverse wildlife. The main elevator core on each level of the new facility is built to look like a tree growing through the center of the building, clad in reclaimed old growth redwood salvaged from the deconstructed Moffett Field hangar in Mountain View, California.

Aspects of California's ecosystems are also part of the foundation for the building's visual "way-finding" system, implemented to help direct people through the building. Stanford University ecologists and patients at the existing Packard Children's Hospital helped select two animal "ambassadors" native to each floor's eco-region. Sculptures of them are tucked into stone niches along the main entrance and are repeated near the elevators and in colorful signs on each floor, helping families find their way around. Patients — and their siblings — also helped the design committee select interactive play structures for the hospital's gardens and large animal structures that serve as directional landmarks on each floor. Artist Sherri Warner Hunter conducted workshops during which patients created crayon and oil pastel drawings of rocky shore creatures, and the drawings have been turned into mosaics that are inset on the underside of several of the play structures and furniture in the garden.

"This is a Northern California hospital in a place where people value preservation of species and nature. It was important to create a building that exhibited stewardship of those values," Guenther said.

But an element of whimsy fit for children remains. At first, the inclusion on the third floor of a life-size sculpture of a pair of hadrosaurs — the only known dinosaurs to live in Northern California — worried parents on the design committee. "We were concerned that a dinosaur would be scary to little kids," Flynn recalled. So at the suggestion of the design committee, the dinosaurs are wearing bunny slippers to make them look more friendly.

Indoor playrooms on each floor, designated by age group, provide spaces for pet therapy, arts and crafts, group games and other activities that involve the whole family.

"There is endless evidence that supports the medical need for healing elements in the hospital. But at the end of the day, what makes it work is that it feels very human. What we wanted was an expansion of Lucile Packard's original vision that would not lose the charm and the humanity of the original," Guenther said.

"As a parent who has had a sick child, any time you step foot into a hospital it brings back a rush of emotions. Some good, some challenging," Flynn said. "For me, despite the difficult memories, I always had this feeling that the hospital was a pleasant place to be and I tend to get filled with an overwhelming amount of gratitude for that. I keep envisioning my son in the new space at 2 and 3 years old. He would have absolutely loved the new garden, the sculptures, the opportunity for exploration."

Wayman echoed that: "Parents bring the lived experience with them. They've walked the walk with their children. While care teams' lived experience is providing care and they have an invaluable perspective on the safety and efficiency of the new design, families look at it with heart. And no one else can do that." **ISM**

LESLIE WILLIAMSON

The Dunlevie Garden occupies the courtyard between the new and the original hospital buildings.

Ethical

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existing ability levels?

Bodies fail but minds work

"For some of these patients, if all they have left is, say, the ability to move one finger or to move their assistive device or they still have the ability to raise an eyebrow as a way to communicate, how can I say that maintaining that is not just as worthy as treating a baby to prevent another disability?" Burgart said.

That's especially difficult because SMA patients don't lose cognitive function, she said. Their bodies are failing them, but their minds still work.

Finally, the cost of treatment looms large not only for patients but also for institutions providing care, with institutional mission playing into every decision.

"If you are interested in making money, you can cherry pick your patients and only take patients who have specific types of insurance, where you'll get a great reimbursement back and can make a lot of money," Burgart said. "But if your mission is to provide the best possible care to your patients, then making money is nowhere near the No. 1 goal. However, if you just treat everyone, irrespective of these issues, and don't think ahead, you can bankrupt your hospital, and then you can't provide any care to anyone. And that's certainly not in the mission of a pediatric hospital."

STEVE FISCH

Alyssa Burgart, medical director of clinical ethics at Lucile Packard Children's Hospital Stanford, is the lead author of an article on ethical questions about how a drug for spinal muscular atrophy is being used.

David Magnus, PhD, director of the Stanford Center for Biomedical Ethics and professor of medicine and of biomedical ethics, said those concerns resonate beyond treating SMA patients, who represent a relatively small group of people, because competition is fierce for resources to treat patients with any number of illnesses for which new and more expensive treatments are emerging. That forces hospitals to make difficult priority decisions.

'Resources are finite'

"Those issues play out in the hospital every day because resources are finite. Beds are scarce, staff is scarce, equipment, surgical space and research resources are all scarce," said Magnus, a co-author of the article. "What are you going to decide not to do?"

There is some financial relief for patients through a Biogen program called SMA360, which helps patients navigate the treatment process and covers costs for some patients. Relief could also come as new treatments — and resulting market competition for nusinersen — emerge, Burgart said. Several SMA treatment trials are in progress, but the community is especially tracking a single-dose gene therapy that, if approved, would have its own cost and treatment implications.

In their article, the authors stressed the need for clear communication among stakeholders about all the issues they considered, especially so patients are well-informed about risks that might not be known yet. For now, they wrote, researchers and clinicians will continue to share any new data about nusinersen use in SMA patients to inform future decisions, including how broadly treatment should be pursued.

"If it's too liberal, you treat patients who won't benefit, and all they incur is more risk. And if you make it too narrow, you never figure out that you can actually accomplish more," Burgart said. "I think the only solution is to treat as broadly as you can, continue to gather data and really continue to look at it in a detailed and thoughtful way that helps patients the most."

Other co-authors of the article are from the Feinberg School of Medicine at Northwestern University; the University of Colorado School of Medicine, Harvard Medical School and the Perelman School of Medicine at the University of Pennsylvania. **ISM**

CD22

continued from page 1

Fifteen of the 21 patients in the phase-1 study had previously either relapsed or failed to respond to anti-CD19 CAR T-cell treatment, which is currently used only when all other therapies have failed.

Potential for a potent new treatment

"This is the first time that we've seen response rates anything like we achieved when we were first testing the CD19 CAR T therapy," said Crystal Mackall, MD, the associate director of Stanford's Cancer Institute and director of the Parker Institute for Cancer Immunotherapy at Stanford. "We were all a little worried that we wouldn't find anything comparable. But this study gives hope to the idea that there may be another similar, very potent treatment." Researchers hope that targeting CD19 and CD22 simultaneously may result in a powerful therapy — one that cancer cells are unable to evade.

Mackall, professor of pediatrics and of internal medicine, is the senior author of the study, which was published online Nov. 20 in *Nature Medicine*. Terry Fry, MD, a pediatric hematologist and oncologist at the National Cancer Institute, is the lead author and led the conduct of the study at the institute.

B-cell acute lymphoblastic leukemia is the most common cancer in children, and it's usually successfully treated with chemotherapy. However, patients who don't respond to initial treatment, or whose cancer recurs after a successful remission, often have a much poorer prognosis.

CAR T-cell therapy relies on a patient's own T cells — a type of immune cell that can be a powerful killing machine. Researchers genetically modify the T cells to recognize specific molecules on the cancer cells' surfaces and kill the cells. Some long-term remissions have followed treatment with the CD19-targeted treatment. But patients whose cancer cells don't express CD19, or which tamp down their expression to evade the treatment, either don't respond or can relapse. Mackall and her colleagues wondered if there was another molecule on the cancer cells that could also be a good target. Her laboratory developed a novel CAR T-cell targeting CD22 to test this idea.

> The new therapy genetically modifies a patient's T cells.

The phase-1, dose-escalation study enrolled patients ages 7 to 30 with B cell acute lymphoblastic leukemia who received varying doses of the anti-CD22 CAR T-cell therapy. Each of the participants had either not responded to or relapsed after bone-marrow transplants, and 10 of the 15 patients who had already undergone CD19-targeted treatment no longer expressed any CD19 on the surface of their cancer cells.

Median remission of six months

At the lowest dose level, one in six patients achieved complete remission after treatment with the anti-CD22 CAR T cells. However, when the researchers escalated the dose to the next level in the study, 11 of 15 patients, or 73 percent, entered remission. The therapy was also relatively well-tolerated by the recipients.

The remissions lasted a median of six months; three patients remain in complete remission at six, nine and 21 months after the therapy. When the researchers investigated further, they learned that cancer cells in those patients who had relapsed had begun expressing lower-than-normal levels of CD22 on their surfaces.

"The take-home message is that we've found another CAR T-cell therapy that displays high-level activity in this phase-1 trial," said Mackall. "But the relapse rate was also high. So this forces the field to get even more sophisticated. How much of a target is needed for successful, long-lasting treatment? What happens if we target both CD19 and CD22 simultaneously?"

Fry and Mackall are already tackling the last question by testing a CAR T cell that recognizes both CD19 and CD22. They've confirmed that this T cell can kill cancer cells in the laboratory dish and in animal models, and they're testing it in a new clinical trial that has opened at Stanford and will open soon at NCI.

Robbie Majzner, MD, an instructor of pediatric oncology at Stanford, and researchers at the National Institutes of Health also co-authored the study.

The work was supported by the NIH, the St. Baldrick's Foundation and Stand Up 2 Cancer.

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

Stanford faculty receive grants from state stem cell agency

By Krista Conger

The governing board of the California Institute for Regenerative Medicine awarded about $6 million to three School of Medicine researchers on Nov. 30. One award is meant to support translational research that has already shown early stage promise; the other two are smaller, proof-of-principle grants meant to allow researchers to test potentially important ideas in the stem cell field at the earliest stages of discovery.

Anthony Oro, MD, PhD, professor of dermatology, received $5.6 million to support his work in developing new treatments for children with a blistering skin disease. The award will be used to develop technologies necessary to scale up production of a patient's own genetically corrected induced pluripotent stem cells to clinically useful levels.

"Our team will work with the newly formed Stanford Center for Definitive and Curative Medicine and the Laboratory for Cell and Gene Medicine to develop a clinically robust and widely available treatment," Oro said. "We hope our efforts will also facilitate other normal and genetically corrected tissue replacement therapies that the center aims to develop at Stanford."

Two other faculty members — assistant professor of medicine Guillem Pratx, PhD, and professor of genetics Hiromitsu Nakauchi, MD — received about $235,000 each as part of the agency's Discovery Inception grant program. Pratx will use the award to develop a sensitive and noninvasive way to track the movement and location of stem cells injected into the body, and Nakauchi is working to develop novel ways to grow blood stem cells outside the body for study and transplantation.

"Exploring and testing new ideas increases the chances of finding treatments for patients with unmet medical needs. Without [the institute's] support many of these projects might never get off the ground," said Maria Millan, MD, president and CEO of the institute, in a statement. "That's why our ability to fund research, particularly at the earliest stage, is so important to the field as a whole."

In total, the agency awarded about $16.4 million at the meeting to support 17 projects. **ISM**

Study links common male medical condition, vascular disease

By Nicoletta Lanese

Men who suffer symptoms from varicoceles, enlarged veins in the scrotum, are more likely to develop vascular disease and metabolic disease, such as diabetes, according to a study by School of Medicine researchers.

Michael Eisenberg, MD, assistant professor of urology, and his team mined data from thousands of medical insurance records to see whether the condition, previously linked to infertility, also puts men at higher risk for other health problems.

Their findings were published online Dec. 1 in *Andrology*. Eisenberg is the senior author. Urology resident Nancy Wang, MD, is the lead author.

> "The development of these diseases is usually pretty silent."

About 15 percent of American men are estimated to have varicoceles, dilated veins in the scrotum. The condition is linked to lower sperm levels and testosterone production. It also can cause pain or shrinkage of the testicles, but often results in none of these symptoms and is left untreated.

"To millions of men that are diagnosed with this, a lot of them are told, 'Don't worry about it,'" Eisenberg said.

Varicoceles are treated for infertility and pain, but other risks may be going unchecked. "Varicoceles are associated with low testosterone, and low testosterone in turn is associated with metabolic risks and heart disease," Wang said. No one has connected the dots between varicoceles, testosterone and these conditions before now, she said.

A strong correlation

For the study, Eisenberg's lab dug through a wealth of data housed in the Truven Health Marketscan Commercial Claims and Encounters database, which contains insurance claims filed by 77 million individuals since 1996. Between 2001 and 2009, the researchers identified more than 4,400 reproductive-age men with diagnosed varicoceles. For comparison, the team also looked at men without varicoceles — a group that included both infertile and fertile men, differentiated based on whether they had received infertility screening or a vasectomy.

The team followed the subjects through time, noting their health status up to about three years out from their diagnoses. They monitored whether the men developed metabolic or vascular disorders.

Compared to men without varicoceles, men with the condition had a significantly higher incidence of heart disease, the researchers found. They also had a higher incidence of diabetes and hyperlipidemia, or high concentrations of fat in their blood.

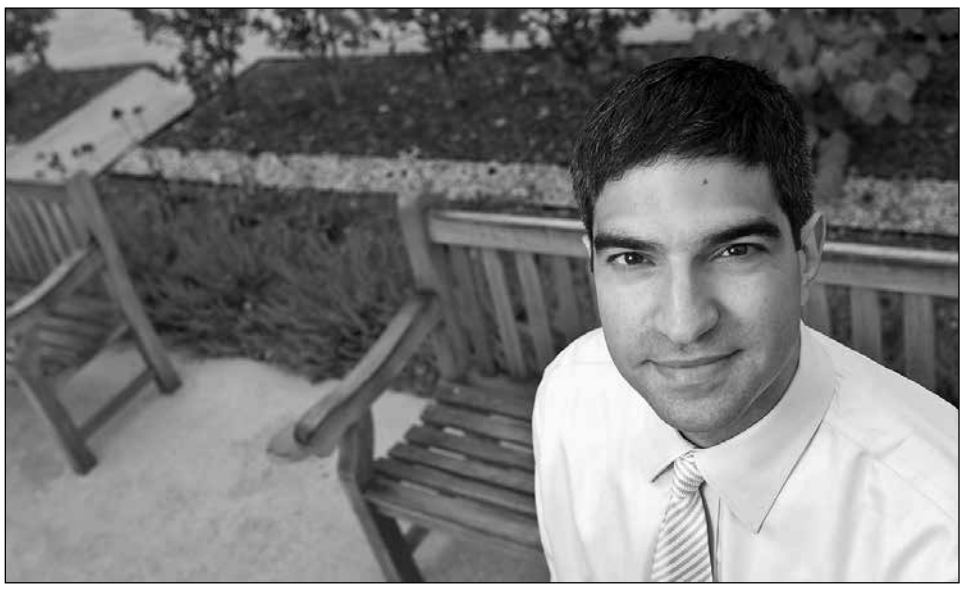
For the most part, only symptomatic varicoceles are treated in the clinic. Asymptomatic varicoceles — those that don't cause pain or impair reproductive function — are only monitored. But the researchers wondered whether both types increase men's risk of developing other diseases and decided to look closer at the data to answer this question.

The team categorized the men with varicoceles by the symptoms they showed, if any, and found that men with asymptomatic varicoceles had no increase in their incidence of heart disease, diabetes or hyperlipidemia relative to men without varicoceles. Only men with symptoms, especially fertility problems and scrotal pain, showed increased risk of developing these diseases.

The results suggest that monitoring for asymptomatic varicoceles remains reasonable, said Eisenberg. "If it's truly asymptomatic, observation remains appropriate," he said.

Although the study produced strong results, it also had limitations, the researchers wrote. The MarketScan Database collects data from a subset of privately insured individuals and may not represent all American men. Those diagnosed with varicoceles are known to have sought out specialist care, which constricts the sample further. In addition, the data lack details about how the varicoceles were diagnosed and how specific symptoms were recorded, and follow-up data was limited to a few years after diagnosis; disease development beyond that window was not available.

STEVE FISCH



Michael Eisenberg and his colleagues found that men who have symptoms associated with enlarged veins in their scrotums are more likely to develop vascular and metabolic disease.

In the last few decades, the rates of cardiac, metabolic and vascular diseases have increased across the United States. This study holds out the possibility that varicoceles may provide a window into men's future health.

"The development of these diseases is usually pretty silent," Wang said. "It's interesting to think about ways to catch disease early, or see risk factors you can identify, to prevent their development or progression."

Going forward, Eisenberg hopes to determine the specific role of varicoceles in metabolic and vascular disease. He said he has uncovered a strong correlation but needs to dig deeper to know if varicoceles play a causative role in these conditions. If they do, the question becomes whether varicocele treatment could help prevent later disease.

"While these results make a strong case that varicoceles are associated with higher risks of cardiovascular diseases and diabetes, we do not yet know if we will need to change our present management for the estimated 17 million U.S. men with varicoceles," said Keith Jarvi, MD, director of the Murray Koffler Urologic Wellness Centre and head of urology at Mount Sinai Hospital in Toronto, who was not involved with the study. "The big question is, 'Is a varicocele just a marker of men's health or could repair of the varicocele actually improve men's health in the long term?'"

Other Stanford co-authors of the study are urology resident Kai Dallas, MD; Laurence Baker, PhD, professor of health research and policy; and statistical programmer Shufeng Li.

The study did not receive outside funding. Stanford's Department of Urology helped to support the work. **ISM**

Gut

continued from page 1

Over the past 15 years, researchers have shown that the composition of a person's gut microbiome can alter their risk for all sorts of health problems, from diabetes and heart disease to allergies and depression.

Justin Sonnenburg

Michael Fischbach

Dylan Dodd

One reason these tiny microbes have such an outsized effect: They can produce molecules known as metabolites that enter the bloodstream and circulate throughout the body. Pinning down exactly which molecules are produced by which bacteria, however, and how to alter their levels to change health, has been challenging.

Improving health from the inside

Previous studies have shown that just a few bacteria, including *C. sporogenes*, can break down tryptophan and produce the metabolite known as indolepropionic acid. Studies have also hinted that IPA helps fortify the intestinal wall, letting fewer molecules leak through.

In the new work, the researchers first detailed exactly how *C. sporogenes* produces IPA from tryptophan. They identified a handful of other compounds also produced in the process — 12 metabolites in total, nine of which can accumulate in the blood and three of which are produced only by bacteria. Then, the researchers pinpointed for the first time the genes that *C. sporogenes* requires for the breakdown of tryptophan and metabolism of the resulting molecules. A gene called fldC, they showed, is required for the production of IPA.

Next, the team gave germ-free mice either wild-type *C. sporogenes* — with the ability to produce IPA — or a version of the bacteria that lacked fldC. In mice that received the wild-type bacteria, levels of IPA in the bloodstream were around 80 micromolar; in mice that received the engineered version of the bacteria, IPA was undetectable.

Finally, they looked at how altering the levels of IPA affected the mice. Mice with undetectable IPA, they found, had higher levels of immune cells, including neutrophils, classical monocytes and memory T cells. This suggested activation of two branches of the immune system — the innate and adaptive immune system. In addition, the mice with the engineered version of *C. sporogenes* had more permeable intestines, a defect which is often seen in gut diseases, including inflammatory bowel disease.

Targeting microbes

If the results hold true in humans, said Sonnenburg, it could point toward a new paradigm for treating some diseases: rather than give a compound, such as IPA, physicians may one day be able to tweak levels of bacteria to affect levels of metabolites. For instance, it might be possible to treat inflammatory bowel disease by boosting levels of *C. sporogenes* and ensuring patients eat enough tryptophan.

"This gives us a specific example of how we can target individual microbes and pathways in the gut to change a person's health," Dodd said. "And this is just one example of hundreds or thousands that are likely out there."

> "IPA is just the tip of the iceberg."

The group next plans to study *C. sporogenes* and IPA levels in mice with more complex gut microbiomes — rather than germ-free mice — and begin tracking down other metabolites produced by the gut microbes that may have health effects.

"While providing a stunning example of how a single gut microbe, and a single gene within that microbe, can impact host health, IPA is just the tip of the iceberg," said Fischbach, "The possibility to positively impact human health through microbiome-produced chemicals is tremendous, and we are poised to take big strides and make this a reality."

Other Stanford authors are Matthew Spitzer, PhD, a former graduate student; graduate students William Van Treuren and Bryan Merrill; postdoctoral scholar Andrew Hryckowian, PhD; life science researcher Steven Higginbottom, PhD; Gary Nolan, PhD, professor of microbiology and immunology; adjunct faculty member Anthony Le; and Tina Cowan, PhD, professor of pathology.

Sonnenburg and Fischbach are both members of Stanford ChEM-H.

The study was funded by the National Institutes of Health; the Food and Drug Administration; the Department of Defense; an HHMI-Simons Faculty Scholars Award; a Byers Award in Basic Science; the David and Lucile Packard Foundation; a BASF research grant; and the National Science Foundation.

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

Stanford honors Miguel 'Mike' Alvarez with 2017 Marsh O'Neill Award

By Kathleen J. Sullivan

When a challenging issue arises in the Veterinary Service Center at Stanford, Miguel "Mike" Alvarez, the center's animal care supervisor, is the go-to person for a constellation of researchers — faculty members, postdoctoral scholars, graduate students and staff.

"It doesn't matter whether the issue is related to animal husbandry, animal behavior, regulatory issues or how to determine the sex of a mouse," said Linda Cork, PhD, DVM, professor emeritus of comparative medicine. "Mike not only knows about the needs of laboratory animals, but he quickly understands the scientific goals of the investigators and how to achieve those goals most effectively."

That was one of many accolades bestowed by Stanford professors on Alvarez, winner of the 2017 Marsh O'Neill Award for Exceptional and Enduring Support of Stanford University's Research Enterprise. The annual award was established in honor of Marshall D. O'Neill, who worked at Stanford from 1952 to 1990, when he retired as associate director of the W.W. Hansen Laboratories. O'Neill was the first recipient of the award.

Alvarez joined the Stanford community in 1971. His first permanent position — as an animal caretaker — turned out to be the beginning of a long Stanford career devoted to the animal care and welfare. He was promoted to animal care supervisor in 1987.

The Veterinary Service Center is part of the Department of Comparative Medicine, an academic department in the School of Medicine.

"In the beginning, when the center was known as the Division of Laboratory Animal Medicine, I provided whatever services they needed me to do, such as driving supplies and equipment to satellite facilities, and providing very basic husbandry, such as placing animals into clean cages and providing water and food," he said. "Later, I became an animal care technician. I've taken part in many educational training programs at Stanford, and I've had lots of mentoring from different professors, doctors and veterinarians."

Currently, Alvarez supervises a staff of 12 animal care technicians. He oversees the training of technicians, principal investigators and research personnel on workplace safety, standard operating procedures and internal policies.

"Among my responsibilities, I must be familiar with all animal husbandry standards and regulatory requirements, and must know the standard operating procedures for the various species of animals used in biomedical research," Alvarez said. "I ensure that our programs and facilities comply with the Animal Welfare Act of the U.S. Department of Agriculture, and the standards outlined in the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals. My role requires knowledge of special handling techniques for biohazard, radioactive and infectious materials."

Alvarez said he takes great satisfaction in every aspect of his work — in the science, the medicine, the animal husbandry and "the humanity."

"I love people," he said. "Any time vested in communication and showing compassion to people is well worth it."

Alvarez said he enjoys sharing the knowledge and information he has accumulated along the way with each new wave of graduate students.

"I watch these kids do three or four years of research — sometimes more — and then I get to see the result when they invite me to their thesis presentations," he said. "It's really rewarding."

Alvarez said he was honored — as well as proud and overwhelmed — to be chosen for the O'Neill Award, which he referred to as the "Hall of Fame for Research" at Stanford.

"I can't ask for anything more when it comes to recognition by professors, superiors and mentors for all the years that I have put into Stanford and into my career," he said. "I'm leaving my mark."

Key role in research

"Without Mike's outstanding professionalism and attention to the many details that are required to provide appropriate care of my mice, my research program would not have succeeded," said Robert Malenka, MD, the Nancy Friend Pritzker Professor in Psychiatry & Behavioral Sciences and deputy director of the Stanford Neurosciences Institute.

L.A. CICERO / STANFORD NEWS SERVICE

Miguel Alvarez is the recipient of the 2017 Marsh O'Neill Award.

Krishna Shenoy, PhD, director of the Neural Prosthetic Systems Laboratory and co-director of the Neural Prosthetics Translations Laboratory, which conducts research aimed at providing clinically useful neural prostheses for people with paralysis, said Alvarez has had a direct positive impact on his lab's ability to conduct successful research involving nonhuman primates.

"Mike is in the trenches every day and is an exceptionally dedicated professional, a collaborator, a leader, a mentor and a role model," said Shenoy, a professor of electrical engineering and the Hong Seh and Vivian W. M. Lim Professor.

Since the facility opened in 2010, Alvarez has worked closely with Majeti's lab staff to make sure their experiments in leukemia and blood stem cells proceed smoothly and effectively.

Michael Moseley, PhD, professor of radiology, said that when he introduces himself as the chair of Stanford's Administrative Panel on Laboratory Animal Care, he gets a smile and a happy "so, do you work with Mike?" response.

"I speak for everyone who ever worked in the experimental biomedical field at Stanford when I say that our expertise and reputation worldwide stands on the shoulders of unique individuals like Miguel Alvarez," Moseley said. **ISM**

Seven Stanford Medicine faculty members appointed to endowed positions

DANIEL CHANG, MD, professor of radiation oncology, was appointed the Sue and Bob McCollum Professor, effective Oct. 3. His clinical and research focus is on the treatment of gastrointestinal cancer using a variety of strategies, including stereotactic body radiotherapy, functional imaging and image-guided radiotherapy.

The professorship was created by Sue and Bob McCollum to support a faculty member in the Department of Radiation Oncology. Sue McCollum founded My Blue Dots, a nonprofit organization that supports cancer research. Bob McCollum is chair and CEO of R.S. Hughes Company Inc., a Sunnyvale-based industrial supplier.

HOWARD CHANG, MD, PhD, professor of dermatology, was appointed the Virginia and D.K. Ludwig Professor of Cancer Genomics, effective Oct. 3. His research interests include epigenetics, RNA biology and the regulation of genes that determine cell fate.

The professorship was created to support a researcher who focuses on the biomedical applications of RNA biology. It is one of six professorships established with funding from the estate of Daniel K. Ludwig, a shipping magnate and financier who established the Ludwig Institute for Cancer Research, which encompasses Ludwig Centers at six U.S. institutions, including Stanford.

CHRISTOPHER GARCIA, PhD, professor of molecular and cellular physiology and of structural biology, was appointed the Younger Family Professor, effective Oct. 3. He studies molecular mechanisms of receptor signaling pathways related to immunology and stem cell biology.

The professorship was created by Bill and Brenda Younger to support a basic science faculty member who is conducting biomedical research that could lead to clinical applications of widespread benefit. Bill Younger earned an MBA from Stanford and is a director emeritus of Sutter Hill Ventures. He is a member of the Stanford Medicine cabinet. Brenda Younger is a retired teacher.

AMY LADD, MD, professor of orthopaedic surgery, was appointed the Elsbach-Richards Professor in Surgery, effective Oct. 3. She specializes in hand surgery, and her research focuses on deciphering the progression and improving treatment of common basilar thumb arthritis.

The professorship was created to support a faculty member who specializes in the translation of basic science into the practice of surgery. Robert Herman Elsbach, who owned a confection and champagne distributing business, was a patient of the late Stanford surgeon Victor Richards, MD, who died in 2002. Elsbach also provided support for the Elsbach-Shenson Scholarship Fund for School of Medicine students.

WILLIAM MALONEY, MD, professor and chair of orthopaedic surgery, was appointed the Boswell Professor in Orthopaedic Surgery, effective Oct. 3. His research focuses on understanding why surgically replaced joints fail. His clinical interests include hip and knee replacement surgeries.

The professorship was created to support a renowned faculty member in the Department of Orthopaedic Surgery and to advance orthopaedic surgery research. The funding came from the James G. Boswell Foundation, established in 1947 by Boswell, who founded a farm and agricultural supply business. His son, James W. Boswell, is now president of the foundation, which has been a longtime supporter of medicine at Stanford.

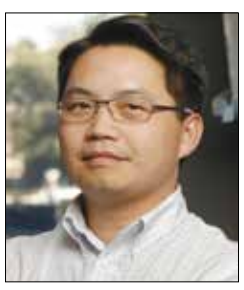
GEOFFREY TABIN, MD, professor of ophthalmology, was appointed the Fairweather Foundation Professor, effective Oct. 3. He is a cornea and cataract specialist whose work focuses on reducing global blindness and developing systems of eye care in Asia and Africa. He is the co-founder of the Himalayan Cataract Project.

The professorship was created to support ophthalmic care, teaching, research and infrastructure development in the field of global ophthalmology. The Fairweather Foundation is managed by Arthur and Joanne Hall. Arthur Hall earned an MBA from Stanford and worked as a hedge fund manager at Valerian Associates. He serves on the board of overseers of the Hoover Institution. Joanne Hall is a retired nurse.

JEROME YESAVAGE, MD, professor of psychiatry and behavioral sciences, was appointed the Jared and Mae Tinklenberg Professor, effective June 15. He directs the Aging Clinical Research Center and is the associate chief of staff for mental health at the Veterans Affairs Palo Alto Health Care System. His interests include geriatric depression, age-associated cognitive decline and sleep disorders related to aging.

The professorship was created by Karla Tinklenberg Jurvetson, MD, and Stephen Jurvetson to honor Karla's parents, Jared Tinklenberg, MD, professor emeritus of psychiatry and behavioral sciences at Stanford, and Mae Tinklenberg. It is intended to support research and clinical work in aging and mental health. **ISM**

Daniel Chang



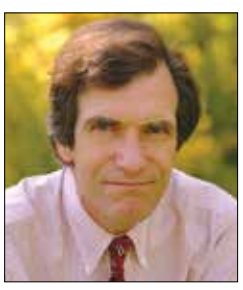
Howard Chang

Christopher Garcia

Amy Ladd

William Maloney

Geoffrey Tabin



Jerome Yesavage