New children’s hospital opens its doors

By Kate DeTrempe

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 Flynn, 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 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.

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 to researchers at the School of Medicine and the National Cancer Institute.

The therapy is similar to but distinct from CD19-directed 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.

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 your-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.

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 Edel, 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.

“Then and there, this is a vivid example of not only how the microbe 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 of the body.
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.

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 them 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 in fact have a circadian clock; the cells exhibit daily oscillations in Per2 expression.

The team then studied what happened over a full 24-hour period in mice in which the cells 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 it do not show major changes in their sleep-wake patterns.

But follow-up experiments by Feldman's team dem- onstrated 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 science still does not know 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 and work during the day, the 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 diabe- tes 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 extra fat in locations such as the liver or muscle can cause problems.

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 scholar Rivka Rivero-Castillo, PhD; and Lijun Ji, PhD; and graduate student Stefanie Monroe.

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

Stanford's Department of Pediatrics also supported the work.

Study: Stem cells that generate fat tissue have circadian clock

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.

By Erin Digitale

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 disease. But the extraordinary cost of the drug, nusinersen, could restrict long-term patient access to it and the ability of clinics and hospitals 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 Penna Burgart, 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 I 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 the 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 $300,000 per year. Other 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 of 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 other care options were palliative care or supportive care, including physical therapy, respiratory help or assistive devices. Most babies developed so quickly that they were placed on ventilators. Some died. Others were placed on full ventilation support, which required the baby to be in the hospital."
Researchers discover second ‘don’t eat me’ signal on cancer cells

By Krista Conger

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 stimulus in preclinical and clinical trials. Researchers now also showed 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. Irving Weissman, a professor of immunology and of developmental biology, and his colleagues 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.

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don’t eat me

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 SIRPα 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 cancer cells. Most cells of the body express MHC class 1 on their surfaces as a way to indiscriminately display parts of many proteins found within the cell — a kind of random sampling of a cell’s interior that provides a window into the 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 hu-

macrophages. These findings help us understand the many ways cancer cells can evade the immune system and we might block these escape pathways.

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

The “don’t eat me” signal is one of the study’s authors is now head of biology at Ab Initio Biotherapeutics Inc. Graduate student Ying Yiu, Benson George, Jonathan Liu, Ying Ma, and former graduate student Kipp Weissman, a professor of pathology and of developmental biology, 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.

The researchers believe that the discovery could lead to new treatments for cancer.

“I am excited about the possibility of a double- or perhaps even triple-pronged therapy,” said Irving Weissman, professor of immunology and of developmental biology, and director of the Ludwig Cancer Center. “However, we need to understand the many ways cancer cells can evade the immune system and 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. “In the future, cancer cells escape from macrophages. These findings help us understand the many ways cancer cells can evade the immune system and we might block these escape pathways.”

Researchers discover second ‘don’t eat me’ signal on cancer cells
Packard continued from page 1

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 create a better environment.’

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, the design committee made sure we would include an experiential journey for patients. They were focused around 30 years ago, people weren't really crafting an experiential journey for patients. They were focused on accommodating the technology — hospitals for machines.’

But the practice of moving patients down into a basement level, the explains, can exacerbate feelings of fear or anxiety that patients — particularly children — can experience below ground and instead enter the basement level, she explains, can exacerbate feelings of being alongside nature as you move through the building, despite being in a hospital. Guenther said. Outside, 3½ 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 over-looking 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 tee-pee.

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 improving 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 minimalist spaces.

‘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 mockups were constructed in an off-site warehouse. Everything was in place, including medical equipment, patient beds, sinks, televisions, light switches, outlets and hand sanitzer 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,” 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 controlling 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 in from a patient or parent perspective,” Flynn said.

The collaboration between providers and parents was key, Wayman explained. ‘Providers learned about parents’ experiences in the hospital, and parents had an opportunity to see how things worked from the provider perspective’. “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...
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 mock-ups, 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 structures and furniture, group games and other activities that involve the whole family.

“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 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 loved 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.”

Stimulating the mind, restoring the body

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

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 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.”

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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?” Burgt said.

He also noted that, especially difficult because SMA patients don't lose cognitive function, she said. Their bodies are failing them, but they're still in the driver's seat.

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

“If you’re 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,” Burgt 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.”

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.

“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 emergence, Burgt said. Several SMA clinical 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 discussed. Yet, for now, they said, researchers and clinicians will continue to share any new data about nusinersen use in SMA patients with other stakeholders, including how broadly treatment should be pursued.

In total, for 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,” Burgt 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.
Gut
continued from page 1

Over the past 15 years, researchers have shown that the composition of a person's gut microbes can alter their risk for all sorts of health conditions, from diabetes and heart disease to allergies and depression. 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, which affect the body. In fact, exactly what molecules are produced by which bacteria, however, and how to alter them — to boost health or decrease disease — still has proponents for the breakdown of tryptophan and metabolism of the resulting molecules. A called FldC, they showed, is required for the production of IPA. Next, the team gave germ-free mice either a wild-type or an engineered version of the bacteria. In 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 other immune cells, including neutrophils, classical monocytes and macrophages. In turn, IPA levels in mice with 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.

“IPA is just the tip of the iceberg.”

“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 Hyrkonen, 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 Scholar 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.

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.

“Study links common male condition, vascular disease

By Nicoletta Lanese

Men who suffer symptoms from varicoceles, enlarged veins in the scrotum, are more likely to develop vascular and metabolic disease, such as diabetes, according to a new 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.

For the study, Eisenberg’s lab dug through a wealth of data housed in the Truven Health Markescan 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 decreased 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.

“IPA is just the tip of the iceberg.”

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When a challenging issue arises in the Veterinary Service Center at Stanford, Miguel “Mike” Alvarez, the center’s animal caretaker, is the go-to person for the constellation of researchers — faculty members, post-doctoral scholars, graduate students and staff. “I first became involved in animal care when I was introduced 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 caretaker in 1987.

The Veterinary Service Center is part of the Department of Pathology and Immunology, 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 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 animal husbandry, animal behavior, regulatory issues and how to determine the sex of a mouse,” Alvarez said. “I understand the scientific goals of the investigators and how to achieve those goals most effectively.”

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