INSIDE STANFORD MEDICINE

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A pediatric emergency physician discusses what families should know about concussions in children and teenagers.

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New curriculum expands opportunities

By Julie Greicius

NEIL GESUNDHEIT

Daniel Bernstein (seated, left) and Paul Berg explain the Discovery Curriculum to new medical students at Berg Hall during orientation week.

A new curriculum at the School of Medicine is transforming the way medical students learn and prepare for careers in clinical care and scientific investigation.

The Discovery Curriculum resulted from a three-year review of the curriculum that involved more than 100 faculty, staff and students. The goal was twofold: first, to create opportunities and flexibility for students' long-term research, personal growth, exploration and discovery; and second, to improve the quality of coursework and teaching, and to close curricular gaps that were identified during the review process.

"The students, faculty and Nobel laureates who developed our Discovery Curriculum are true innovators in medical education," said Lloyd Minor, MD, dean of the School of Medicine. "Their efforts will facilitate pursuits of fundamental discovery that further our precision health vision, provide our students with a more flexible and distinctive learning experience, and expedite the preparation of physician-scientists to become leaders in biomedical investigation."

Physician-scientists balance their time between research and clinical care. They usually work at academic medical centers, in settings where their clinical practice can inform their research and vice versa.

Expediting physician-scientist training is more important than ever, given the dwindling number of clinical investigators in the workforce, said PJ Utz, MD, professor of immunology and rheumatology and associate dean for medical student research. "Over the last 15 years, the number of physician-scientists aged in their 40s went from about 7,000 down to about 4,000," Utz said. "And the numbers of those who are in their 60s, 70s and 80s increased. By our analysis, close to 200 additional physician-scientists need to be trained every year than we are currently graduating across the nation."

A 2014 report from the National Institutes of Health detailed the challenges weighing on the physician-scientist workforce — such as longer training times and increasing educational debt — and noted that "the largest group of NIH-funded U.S. physician-scientists continue to be those who hold an MD as their only professional degree." The report highlighted the value of physician-scientists, noting that those who both see patients and perform research can "help identify the mechanisms of disease, as well as apply the findings of basic science to patient care."

The School of Medicine's new curriculum is designed to introduce research to medical students earlier in their training to support their goals for learning and discovery without requiring them to spend the seven to eight years needed to See CURRICULUM, page 7

Progress, priorities and challenges are focus of Stanford Medicine leadership at annual event

By Julie Greicius

Hailing Stanford Medicine as "the epicenter of biomedical discovery for the world," Lloyd Minor, MD, dean of the School of Medicine, encouraged audience members gathered Sept. 17 at the State of Stanford Medicine event to strive to make sure that statement remains true decades from now.

Discussing the basic sciences, Minor said the goal is "to maintain a vibrant and world-class, leading discovery engine here at Stanford."

The event drew about 500 people to Berg Hall, in the Li Ka Shing Center for Learning and Knowledge, to listen to the three leaders of Stanford Medicine — Minor, Stanford Health Care CEO David Entwistle and Stanford Children's Health interim CEO Dennis Lund, MD — share their insights on the progress and priorities of the three institutions. Hundreds more watched a livestream of the event.

ROD SEARCEY

(From left) Leslee Subak, chair of obstetrics and gynecology, moderated a panel discussion with Stanford Medicine leaders Dennis Lund, David Entwistle and Lloyd Minor at the State of Stanford Medicine event.

Minor opened the event with a discussion of the integrated strategic plan, which unites Stanford Medicine's three entities in a shared vision of the future that is both human-centered and discovery-led. He announced a new awards program, the Integrated Strategic Plan Star Awards, to recognize Stanford employees who contribute to the success of the plan. He also encouraged more feedback about the plan itself. "Moving forward, we're really looking to you for engagement, feedback and involvement in the execution of the plan," he said.

Working together with families

Minor welcomed technology entrepreneur Matthew Wilsey to join Lund and Entwistle onstage. Wilsey's young daughter, Grace, See LEADERS, page 6

Humans bombarded by microorganisms, chemicals, study finds

By Hanae Armitage

We are all exposed to a vast and dynamic cloud of microbes, chemicals and particulates that, if visible, might make us look something like Pig-Pen from *Peanuts*.

Using a re-engineered air-monitoring device, scientists from the School of Medicine have peered into that plume and discovered a smorgasbord of biological and chemical minutia that swirl in, on and around us. Their findings show, in unprecedented detail, the variety of bacteria, viruses, chemicals, plant particulates, fungi, and even tiny microscopic animals that enter our personal space — a bombardment known as the human "exposome."

"Human health is influenced by two things: your DNA and the environment," said Michael Snyder, PhD, professor and chair of genetics at Stanford. "People have measured things like air pollution on a broad scale, but no one has really measured biological and chemical exposures at a personal level. No one really knows how See EXPOSOME, page 5

Cheap testing spurs next of kin to assess own cancer risk

By Krista Conger

An online initiative offering low-cost genetic testing to relatives of people with genetic mutations that increase their risk of cancer encourages the "cascade" testing that can help to identify healthy people at risk of the disease, according to a new study by researchers at the School of Medicine and Color, a health services company that provides genetic testing.

The study of more than 700 people bearing one of 30 cancer-associated mutations found that nearly half of a patient's first-degree relatives (think mother, father, siblings and children) chose to undergo testing when contacted by a genetic testing laboratory and offered a chance to have their own genes sequenced for about $50 — about one-tenth the standard cost. Furthermore, about 12 percent of those found to have the same mutation as the original patient then went on to invite additional relatives to be tested.

STEVE FISCH

Allison Kurian and her colleagues found that online outreach, coupled with low-cost testing, significantly increased the proportion of cancer patients' relatives who chose to undergo genetic testing for cancer-associated mutations.

Although not everyone with a cancer-associated mutation will go on to develop the disease, the knowledge that one is a carrier can help people and their doctors make informed health care decisions while they are still healthy. For example, women with BRCA1 or BRCA2 mutations who have a vastly increased risk of developing breast or ovarian cancers may choose to undergo prophylactic mastectomies or have their ovaries removed. Other types of mutations, such as those that increase one's risk of colon cancer, may indicate the need for increased or more frequent screening.

"We've found that this approach has been remarkably successful in overcoming traditional barriers to reaching and testing a patient's relatives," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "The results have been very striking, as traditional approaches to cascade testing result in only about 30 percent of relatives undergoing testing."

Kurian shares senior authorship of the research, which was published Sept. 18 in the *Journal of the National Cancer Institute*, with Alicia Zhou, PhD, who is head of research at Color, based in Burlingame, California. Jennifer Caswell-Jin, MD, instructor of medicine at Stanford, and Anjali Zimmer, PhD, a technical writer from Color, are the lead authors of the study.

Growing interest in genetic tests

Increasingly, newly diagnosed cancer patients are turning to genetic testing in a quest to understand why they've developed the disease. The discovery of a disease-associated mutation can help drive treatment decisions and provide clues as to the cancer's origin. But there's another important, often overlooked benefit: The test results can help a patient's healthy first-degree relatives assess their own genetic risk for cancer. About 50 percent of these relatives could be expected to harbor the same mutation as the patient, even if they haven't developed cancers themselves.

However, this kind of cascade testing, in which a positive result in a cancer patient triggers waves of genetic testing among the patient's relatives, remains relatively rare — in part because physicians are often prohibited from directly contacting a patient's relatives, and people reeling from their own recent diagnosis may not immediately consider the health implications for their loved ones. Testing can also be expensive and is not always covered by insurance.

Kurian and her colleagues wondered if there was an easier way to reach potential carriers. They evaluated the first year of a family testing program in which people found to harbor one of 30 cancer-associated genes were encouraged to provide the testing laboratory with email addresses for their first-degree relatives. The laboratory then contacted the relatives to provide more information via a web portal and invite them to be tested for an out-of-pocket cost of $50.

"One unique thing about this study is that it isn't focused on any single gene," Caswell-Jin said. "These participants were carriers of mutations in any of 30 different genes, some of which are very strongly associated with the development of specific cancers. Because about half of a patient's first-degree relatives are also likely carriers of the same mutation, cascade testing has significant public health implications for early cancer detection and even prevention."

To conduct the study, the researchers invited carriers of one of 30 cancer-associated mutations, identified by any one of several certified genetic testing laboratories, and their relatives to participate in the family testing program. They reached possible participants through the use of online advertising, notices in physicians' clinics or at group meetings for families with hereditary cancers.

From September 2016 to September 2017, 1,101 people — 741 people who carried the mutation themselves, and 360 relatives of the carriers — opted to participate in the program. Together, the original participants then invited 2,280 of their relatives to also be tested. Nearly half of those invited underwent testing themselves within the study's follow-up period.

Different mutations also identified

As expected, about half of the tested relatives were also carriers. About 12 percent of these people then used the family testing program to invite additional first-degree relatives to be tested.

"Although this was potentially lower than we might have expected, in many cases it was due to the fact that there were no more first-degree relatives in the family to test," Caswell-Jin said.

Surprisingly, the researchers found that about 5 percent of relatives tested carried cancer-associated mutations that differed from those of their patient relatives.

"These pathogenic mutations were totally unexpected and suggest that this may reflect the prevalence in the general population of known cancer-associated mutations," Kurian said. "It addresses a long-standing question in the field about what we might find if we routinely tested everyone."

The researchers emphasize that, regardless of how people are contacted to be tested, it is important to involve a genetic counselor to interpret test results and direct mutation carriers to appropriate health care services.

"This is such an exciting era," Caswell-Jin said. "We expect the proportion of people undergoing genetic testing for disease-associated mutations will continue to increase. We need to make sure they get the support they need to understand their results, and to encourage additional support and follow-up."

"We are very engaged in learning how to most effectively implement genetic testing, particularly in a broad population," Kurian said. "We are eager to pursue this finding further and to understand how we can improve on this new model of cascade testing."

Another Stanford author of the study is senior genetic counselor Kerry Kingham. Kurian is a member of the Stanford Cancer Institute.

The research was supported by the BRCA Foundation, the Damon Runyon Cancer Research Foundation and Color.

Kurian has received research funding from Myriad Genetics for an unrelated project.

Stanford's departments of Medicine and of Health Research and Policy also supported the work. ISM

Stanford Children's Health joins forces with Children's Health Council to help teens with mental health challenges

By Samantha Beal

Stanford Children's Health and the Children's Health Council in Palo Alto have launched a joint program to offer intensive outpatient therapy to teens ages 14-18 who are struggling with suicidal thoughts and behaviors, self-harm or other severe mental health challenges.

The program is called RISE, which stands for "reaching interpersonal- and self-effectiveness." It's co-led by Michele Berk, PhD, assistant professor of psychiatry and behavioral sciences at the Stanford School of Medicine. Berk brings to the program extensive research and clinical expertise in dialectical behavioral therapy, a specialized intervention for individuals with suicidal or self-harming behaviors, or both. The new program is based on an existing intensive outpatient program at CHC.

According to Antonio Hardan, MD, chief of child and adolescent psychiatry at Lucile Packard Children's Hospital Stanford, the program is filling a crucial gap in providing a comprehensive continuum of care for teens facing mental health challenges.

"The availability of an intensive outpatient program is critical for teens with different levels of severity of mental health problems," said Hardan, who is also a professor of psychiatry and behavioral sciences at the School of Medicine. "Stanford and CHC have complementary expertise that make this program truly valuable for patients and families."

The treatment covers the often overlooked but essential "middle ground" between weekly outpatient therapy and hospitalization, and provides support for patients who are transitioning between the two. The program also offers a critical step-down option for teens who have been discharged and are returning home from psychiatric inpatient or residential stays.

In addition to Berk, child psychologist Stephanie Clarke, PhD, a clinical instructor of psychiatry and behavioral sciences at Stanford, joins licensed clinicians from CHC who were trained through the Linehan Institute to provide all components of a comprehensive dialectical behavioral therapy program for adolescents. (Marsha Linehan, PhD, developed the therapy, a type of cognitive behavioral therapy, to treat borderline personality disorder. Dialectical behavioral therapy is now also used to treat other types of psychological disorders.)

Therapy offered for teens, families

RISE is housed at the CHC's headquarters in Palo Alto, where participants attend a 12-week course for four days each week after school. After-hours phone coaching is available 24/7. The program includes individual therapy, a multi-family skills group and family therapy. Medication

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STANFORD MEDICINE

Study IDs stem cell that gives rise to new bone, cartilage in humans

By Krista Conger

A decade-long effort led by School of Medicine scientists has been rewarded with the identification of the human skeletal stem cell.

The cell, which can be isolated from human bone or generated from specialized cells in fat, gives rise to progenitor cells that can make new bone, the spongy stroma of the bone's interior and the cartilage that helps our knees and other joints function smoothly and painlessly.

The discovery allowed the researchers to create a kind of family tree of stem cells important to the development and maintenance of the human skeleton. It could also pave the way for treatments that regenerate bone and cartilage in people.

"Every day children and adults need normal bone, cartilage and stromal tissue," said Michael Longaker, MD, professor of plastic and reconstructive surgery. "There are 75 million Americans with arthritis, for example. Imagine if we could turn readily available fat cells from liposuction into stem cells that could be injected into their joints to make new cartilage, or if we could stimulate the formation of new bone to repair fractures in older people."

A paper describing the finding was published online Sept. 20 in *Cell*.

Longaker, the Deane P. and Louise Mitchell Professor in the School of Medicine and the co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, is the senior author. The lead authors are Charles K.F. Chan, PhD, assistant professor of surgery; medical student Gunsagar Gulati, MD; Rahul Sinha, PhD, instructor of stem cell biology and regenerative medicine; and research assistant Justin Vincent Tompkins.

'True, multipotential, self-renewing'

The skeletal stem cells are distinct from another cell type called the mesenchymal stem cell, which can generate skeletal tissues, fat and muscle. Mesenchymal stem cells, which can be isolated from blood, bone marrow or fat, are considered by some clinicians to function as all-purpose stem cells. They have been tested, with limited success, in clinical trials and as unproven experimental treatments for their ability to regenerate a variety of tissues. Recently, three elderly patients in Florida were blinded or lost most of their sight after mesenchymal stem cells from fat were injected into their eyes as an experimental treatment for macular degeneration.

"Mesenchymal stem cells are loosely characterized and likely to include many populations of cells, each of which may respond differently and unpredictably to differentiation signals," Chan said. "In contrast, the skeletal stem cell we've identified possesses all of the hallmark qualities of true, multipotential, self-renewing, tissue-specific stem cells. They are restricted in terms of their fate potential to just skeletal tissues, which is likely to make them much more clinically useful."

Skeletal regeneration is an important capability for any bony animal evolving in a rough-and-tumble world where only the most fit, or the fastest-healing, are likely to survive very long into adulthood. Some vertebrates, such as newts, are able to regenerate entire limbs if necessary, but the healing ability of other animals, such as mice and humans, is more modest. Although humans can usually heal a bone fracture fairly well, they begin to lose some of that ability with age. And they are completely unable to regenerate the cartilage that wears away with age or repetitive use. Researchers have wondered whether the skeletal stem cell could be used clinically to help replace damaged or missing bone or cartilage, but it's been very difficult to identify.

Adult stem cells lineage-restricted

Unlike embryonic stem cells, which are present only in the earliest stages of development, adult stem cells are thought to be found in all major tissue types, where they bide their time until needed to repair damage or trauma. Each adult stem cell is lineage-restricted — that is, it makes progenitor cells that give rise only to the types of cells that naturally occur in that tissue. For our skeleton, that means cells that make bone, cartilage and stroma.

Chan, Longaker and their colleagues had hoped to use what they learned from identifying the mouse skeletal stem cell to quickly isolate its human counterpart. But the quest turned out to be more difficult than they had anticipated. Most cell isolation efforts focus on using a technology called fluorescence activated cell sorting to separate cells based on the expression of proteins on their surface. Often, similar cell types from different species share some key cell surface markers.

But the human skeletal stem cell turned out to share few markers with its mouse counterpart. Instead, the researchers had to compare the gene expression profiles of the mouse skeletal stem cell with those of several human cell types found at the growing ends of developing human bone. Doing so, they were able to identify a cell population that made many of the same proteins as the mouse skeletal stem cell. They then worked backward to identify markers on the surface of the human cells that could be used to isolate and study them as a pure population.

"This was quite a bioinformatics challenge, and it required a big team of interdisciplinary researchers, but eventually Chuck and his colleagues were able to identify a series of markers that we felt had great potential," Longaker said. "Then they had to prove two things: Can these cells self-renew, or make more of themselves indefinitely, and can they make the three main lineages that comprise the human skeleton?"

The researchers showed that the human skeletal stem cell they identified is both self-renewing and capable of making bone, cartilage and stroma progenitors. It is found at the end of developing bone, as well as in increased numbers near the site of healing fractures. Not only can it be isolated from fracture sites, it can also be generated by reprogramming human fat cells or induced pluripotent stem cells to assume a skeletal fate.

Michael Longaker

'The perfect niche'

Intriguingly, the skeletal stem cell also provided a nurturing environment for the growth of human hematopoietic stem cells — or the cells in our bone marrow that give rise to our blood and immune system — without the need for additional growth factors found in serum.

"Blood-forming stem cells love the interior of spongy bone," Chan said. "It's the perfect niche for them. We found that the stromal population that arises from the skeletal stem cell can keep hematopoietic stem cells alive for two weeks without serum."

By studying the differentiation potential of the human skeletal stem cell, the researchers were able to construct a family tree of stem cells to serve as a foundation for further studies into potential clinical applications. Understanding the similarities and differences between the mouse and human skeletal stem cell may also unravel mysteries about skeletal formation and intrinsic properties that differentiate mouse and human skeletons.

"Now we can begin to understand why human bone is denser than that of mice, or why human bones grow to be so much larger," Longaker said.

In particular, the researchers found that the human skeletal stem cell expresses genes active in the Wnt signaling pathway known to modulate bone formation, whereas the mouse skeletal stem cell does not.

The ultimate goal of the researchers, however, is to find a way to use the human skeletal stem cell in the clinic. Longaker envisions a future in which arthroscopy — a minimally invasive procedure in which a tiny camera or surgical instruments, or both, are inserted into a joint to visualize and treat damaged cartilage — could include the injection of a skeletal stem cell specifically restricted to generate new cartilage, for example.

"I would hope that, within the next decade or so, this cell source will be a game-changer in the field of arthroscopic and regenerative medicine," Longaker said. "The United States has a rapidly aging population that undergoes almost 2 million joint replacements each year. If we can use this stem cell for relatively noninvasive therapies, it could be a dream come true."

Longaker is a member of the Stanford Child Health Research Institute, the Stanford Cardiovascular Institute, the Stanford Cancer Institute and Stanford Bio-X.

Other Stanford authors are CIRM scholars Michael Lopez, Rachel Brewer, and Lauren Koepke; former graduate students Ava Carter, PhD, and Ryan Ransom; graduate students Anoop Manjunath and Stephanie Conley; former postdoctoral scholar Andreas Reinisch, MD, PhD; research assistant Taylor Wearda; clinical assistant professor of plastic and reconstructive surgery Matthew Murphy, MD; medical student Owen Marecic; former life sciences researcher Eun Young Seo; former research assistant Tripp Leavitt, MD; research assistants Allison Nguyen, Ankit Salhotra, Taylor Siebel and Karen Chan; instructor of stem cell biology and regenerative medicine Wan-Jin Lu, PhD; postdoctoral scholars Thomas Ambrosi, PhD, and Mimi Borrelli, MD; orthopaedic surgery resident Henry Goodnough, MD, PhD; assistant professor of orthopaedic surgery Julius Bishop, MD; professor of orthopaedic surgery Michael Gardner, MD; professor of medicine Ravindra Majeti, MD, PhD; associate professor of surgery Derrick Wan, MD; professor of surgery Stuart Goodman, MD, PhD; professor of pathology and of developmental biology Irving Weissman, MD; and professor of dermatology and of genetics Howard Chang, MD, PhD.

Researchers from the Medical University of Graz in Austria, RIKEN in Japan and the University of California-San Diego also contributed to the study.

The study was supported by the National Institutes of Health, the California Institute for Regenerative Medicine, the Howard Hughes Medical Institute, the Oak Foundation, the Hagey Laboratory, the Pitch Johnson Fund, the Gunn/Oliver Research Fund, a Siebel Fellowship, a PCFYI Award, Stinehart/Reed, the Deutsche Forschungsgemeinschaft and the Ellenburg Chair.

Stanford's Department of Medicine also supported the work.

The researchers have a pending patent for the isolation, derivation and use of human skeletal stem cells and their downstream progenitors. **ISM**

RISE

continued from page 2

management is also provided by psychiatrists and Stanford child and adolescent psychiatry fellows for the duration of the program.

According to Berk, who was one of the principal investigators of a large clinical trial of dialectical behavioral therapy that was recently published in *JAMA Psychiatry*, the therapy is currently the only well-established, evidence-based treatment for decreasing self-harming behavior in youth. Hence, Berk said, the collaboration between CHC and Stanford Children's Health provides "gold standard" treatment for these youth.

In addition to treating young people who have attempted suicide or engaged in self-harming behaviors, the program will also treat those with severe symptoms of anxiety, depression or suicidal thoughts and those who have experienced a significant decrease in functioning at school and at home — e.g., marked decline in grades, school absenteeism — for whom weekly or biweekly outpatient therapy is not effective for symptom reduction and improved functioning.

> "Stanford and CHC have complementary expertise."

A hallmark of dialectical behavioral therapy is its inclusion of parents and guardians in treatment. In RISE, parents and guardians join their teens two times a week in a multifamily skills group, where they learn and practice the skills necessary to manage the teens' symptoms.

"It's critical that parents and guardians learn the skills and feel empowered to support their teens through a time of crisis," said Ramsey Khasho, PsyD, chief clinical officer at CHC and the other co-leader of the program. "We are excited and proud to have developed a joint intensive outpatient program with Stanford Children's Health to provide more teens and families with the best care possible."

Hardan agreed. "Through CHC's experience in the development and implementation of intensive mental health and academic programs and Stanford's expertise in conducting research and providing care for adolescents with suicidal behavior, this program can be transformative for local adolescents who are in need of this level of care," he said.

The RISE program is accepting referrals. Call (650) 688-3625 or email help@chconline.org to refer a patient. **ISM**

5 QUESTIONS

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

What families should know about concussions

Angela Lumba-Brown, MD, first learned about concussions from personal experience.

"I had two concussions playing high school basketball," said Lumba-Brown, a clinical assistant professor of emergency medicine and of pediatrics at the School of Medicine. "I had great doctors who were able to explain to me what I was feeling, which added to my rapidly developing interest in how the brain works."

Knowledge of brain injuries has advanced significantly since those conversations, in part thanks to Lumba-Brown's work. She conducts research on brain injury at the Stanford Concussion and Brain Performance Center, which she co-directs, and treats patients at Stanford Health Care's pediatric emergency department. She is also the lead author of a new set of guidelines from the Centers for Disease Control and Prevention advising clinicians on the diagnosis and treatment of mild traumatic brain injuries, including concussion, in children and teenagers. Published Sept. 4 in JAMA Pediatrics, the new guidelines are based on evidence from over 35,000 scientific studies of brain injury that came out between 1990 and 2015. Specific resources for patients and families also are highlighted in the guidelines. Lumba-Brown spoke with science writer Erin Digitale about what families should know about concussions.

1 What are the warning signs that a child who has bumped their head should be taken to the emergency department or their pediatrician?

LUMBA-BROWN: There are many important warning signs of mild traumatic brain injury that can be difficult to discern from more severe types of brain injuries. These warning signs require evaluation by a clinician right away and include: the child not acting like their usual self, worsening symptoms following injury, headache that becomes severe, unsteadiness or difficulty walking, changes in their speech, seizures, "black-outs" and any excessive sleepiness, dizziness or confusion.

If the mechanism of injury was severe — a car accident or fall from a height, for example — they should also be examined by a clinician. In general, families should exercise caution and come to the emergency department or their doctor if they feel something is not right with their child.

Angela Lumba-Brown

2 The new CDC guidelines recommend changing the terminology we use for concussions. Why?

LUMBA-BROWN: Traditionally, concussion has been considered a type of mild traumatic brain injury in which there is no evidence of hemorrhage on standard neuroimaging. However, other "mild" brain injuries, including those with small amounts of bleeding or bruising of the brain, are treated exactly the same way as concussion. Studies have also shown that there is a different perception about the terms "concussion" and "mild traumatic brain injury" among patients, families and coaches. We want to ensure that we are describing the most medically correct process possible when advising our patients, and hence we are now talking about "mild traumatic brain injury."

3 What should parents expect if their child is being evaluated for a mild traumatic brain injury?

LUMBA-BROWN: The main test we use to evaluate a child for this type of injury is our physical exam, which includes assessment of neurologic function. This exam includes assessing the child's speech and flow of thoughts and emotions, how they move and walk, their coordination, their strength and muscle tone, and the action of facial muscles that can reflect potential problems with cranial nerves, as well as neck injuries or other injuries. Families sometimes expect an imaging test, but the physical exam performed by the doctor is actually the most important test. The doctor may also want to monitor the child for a couple of hours for any change in symptoms that might reflect a more serious process, such as significant bleeding on the brain, which could take time to develop. The new guidelines do not recommend head CT imaging or X-rays for children suspected of having a concussion, since it's important to avoid exposing them to unnecessary radiation.

Families should tell their doctor about any previous head injuries their child has had, as well as any bleeding disorders or other neurologic issues, such as seizure disorders, ventriculo-peritoneal shunts, brain surgeries or neck injuries. Other important medical history to share with the doctor include: history of attention deficit hyperactivity disorder, mood or anxiety disorders, prior issues with their balance, problems with their eyesight, sleep disorders, or a history of migraines. Children with these medical histories may have longer recoveries.

It's important for families to know that many pediatricians or family medicine physicians will manage a child's mild traumatic brain injury. However, in some instances, a doctor may recommend follow-up with specialists.

4 What should families know about the recovery from mild traumatic brain injuries?

LUMBA-BROWN: In most cases, physicians can discharge children from the emergency department after determining that they've suffered a concussion. But physicians need to tell families to return to an emergency department or clinic right away if they see any worsening symptoms. We advise families that their child should take it easy the day following the injury but re-integrate into physical activity as soon as possible. It is common for a child with mild traumatic brain injury to have a headache, nausea and dizziness in the days following their injury. They may not even remember the actual injury or even events surrounding the day of the injury. It is also common for children to have problems focusing and changes in sleep patterns over the next weeks. They could be more emotional or get headaches more easily. Specific symptoms will change as the child is recovering.

The brain needs some stimulation to get blood flow back to the injured areas, so we don't want a child in a dark room, sleeping all day. It's better to maintain the usual routine, maybe with some naps but also some walking, running and playing. Re-integrating into exercise is important for recovery and overall health. However, children should avoid activities that carry risk for re-injury — such as jumping off couches, playing soccer, riding a mountain bike downhill, or jumping on trampolines. Cognitive activities like reading, watching TV or playing on an iPad are OK if they aren't worsening the child's symptoms significantly.

Re-injury is the major risk for a child or teenager with a mild traumatic brain injury. Let's take this example: An injured knee is weaker as it recovers, and a fall or misstep could much more easily re-injure it. The brain is similar: With another blow to the head, a second injury can occur at a lower threshold of impact. That's why clinicians recommend no contact sports during recovery from a mild traumatic brain injury. This can be difficult advice for children who thrive on play; we need to ensure the child understands to the best of their ability why they can't climb trees, head their soccer ball or participate in other activities that could result in re-injury.

Children should see their doctor for a second visit within a week of their injury to assess how they are improving. Their doctor can guide the family about a return to full activity, including contact activity. If a child is not recovering at the expected rate as the month progresses, a brain-imaging test, such as an MRI, may be warranted.

Mild traumatic brain injuries need time to heal, and children need emotional and physical support from their families, teachers and sports coaches to help their recovery and ensure that they aren't overexerted or re-injured.

5 What are the big unanswered questions about concussion and other forms of mild traumatic brain injury?

LUMBA-BROWN: Most children's symptoms begin to improve by about 10 days, but 20 to 30 percent recover much more slowly. The doctor's clinical exam, including evaluation of the child's medical history and current symptoms, flags who may be at risk for slower recovery: For example, more symptoms and more severe symptoms are warning signs. We're now studying how to effectively treat these symptoms.

Research conducted at the Stanford Concussion and Brain Performance Center has identified five main groups of symptoms following concussion: headache or migraine; cognitive symptoms, such as slowed reaction time and difficulty processing information; anxiety and mood symptoms; ocular-motor symptoms, such as blurry vision and trouble with eye-tracking; and vestibular or balance symptoms. But we are just starting to understand how these different groups of symptoms may benefit from specific types of treatment.

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Research on mild traumatic brain injury conducted by Lumba-Brown and others will be discussed April 27 during the first-ever Stanford Sports Concussion Summit at the Arrillaga Family Sports Center. The event will be open to the public. **ISM**

Study shows how head and neck positioning affects concussion risk

By Taylor Kubota

If you're about to run headfirst into something, your reflex might be to tense your neck and stabilize your noggin. But according to a new study by researchers at Stanford, that may not be the best way to stave off a concussion. Instead, the findings suggest that your head's position is more important than whether you are tensing your neck.

It all comes down to how your head accelerates backward after impact, which some think is the major factor controlling concussion risk.

"We found it really interesting that your soft tissue — muscles, ligaments and tendons — isn't doing much to dictate how your head is rotating immediately after an impact," said graduate student Michael Fanton. "Whereas even a few degrees of change in your head-neck angle can really alter how much your head is rotated and therefore, probably, your risk of concussion."

The researchers made their discovery in a model of the human head and neck, but confirmed what they found in a similar model of a woodpecker, which can endure extreme accelerations when pecking holes. It turns out they too may be protected in part by the angle of their pecking.

Modeling a woodpecker's head and neck as part of the study.

The study was published Aug. 20 in *IEEE Transactions on Biomedical Engineering.* Fanton is the lead author. The senior author is David Camarillo, PhD assistant professor of bioengineering.

A big surprise

In a previous study by Stanford researchers, including Fanton and Camarillo, miniature weights were tied to people's heads to tilt them backward. They then monitored how the head moved after participants either relaxed or tensed their necks. From this, they constructed a simple computer model that recreated the way the head tilts forward and backward.

In the new study, Fanton and Camarillo and their fellow researchers ran simulations with this model that replicated low-impact forces and found that tense neck muscles slightly reduced head acceleration. But they also extended those simulations to include higher-force impacts — the kinds that could lead to concussion, such as what someone might experience falling off a bike — with much different results. When looking at fast, hard impacts, it does not seem to matter whether the neck muscles are tensed or relaxed.

"Originally, we thought **See CONCUSSION, page 5**

Exposome

continued from page 1

vast the human exposome is or what kinds of things are in there."

That curiosity — to see, for the first time, what a person's exposure looks like at an individual level and how much it varies among people — was what motivated the study, Snyder said. But studying the exposome also provides an opportunity to clarify environmental influencers of human health that are otherwise obscure, he said. For example, rather than simply blaming pollen, those with seasonal allergies would be able to identify exactly what they're allergic to by monitoring their exposome data and symptoms throughout the year.

The study's findings also reveal information about geographic- and household-chemical spikes and weather-related patterns, and likewise show the wide range of chemical and biological particulates that can be found between individuals — even within a relatively small geographic region, such as the San Francisco Bay Area.

The study was published online Sept. 20 in *Cell*. Snyder is the senior author. Postdoctoral scholar Chao Jiang, PhD; research scientist Xin Wang, PhD; research associate Xiyan Li, PhD; and postdoctoral scholars Jingga Inlora, PhD, and Ting Wang, PhD, are co-lead authors.

'About 70 billion readouts'

For two years, the scientists collected data from 15 participants who traversed more than 50 different locations. Some people were monitored for a month, some for a week, and one (Snyder) for two full years. To capture bits of each individual's exposome, a small device that straps snuggly to the participant's arm "breathes" in tiny puffs of air — about one-fifteenth the volume of an average human breath.

The device, about the size and shape of a large matchbox, accompanies participants everywhere and is equipped with a sub-micron filter that traps particulate matter in the device. The data — bacteria, viruses, chemicals, fungi and anything else sucked up by the device — is brought back to Snyder's lab and extracted for DNA and RNA sequencing, as well as chemical profiling, to identify all the collected organisms and chemicals that the person is exposed to.

This idea — to siphon up bits of an individual's exposome and systematically categorize what's in it — is novel, Snyder said. And it required Jiang to stitch together an entirely new database.

"Scientists had assembled separate bacteria, viral or fungi databases, but to fully decode our environmental exposures, we built a pan-domain database to cover more than 40,000 species," Jiang said. It includes information on bacteria, viruses,

PAUL SAKUMA

Michael Snyder with one of the devices used in the study to capture the micrscopic stuff that enters our personal space.

fungi, animals, plants and more, all organized in a single searchable database.

"We sequenced these samples in incredible detail," said Snyder, who is also the Stanford W. Ascherman, MD, FACS, Professor in Genetics. "No one has ever done a study this deep before. We ended up with about 70 billion readouts."

Parsing particulates

Between participants, Snyder and Jiang found that exposomes could be vastly different, even in a reasonably tight geographic region — in this case, the San Francisco Bay Area. Snyder cited an especially well-controlled portion of the study, in which four participants, including Snyder, were closely monitored over one month, as a case in point.

Each person lived in a distinct region of the San Francisco Bay Area: Palo Alto, Sunnyvale, Redwood City and San Francisco (though the person who lived in Redwood City commuted across the bay to his job). "It turns out, even at very close distances, we have very different exposure profiles or 'signatures,'" Snyder said. These personal signatures are essentially traces of specific fungi, plants, chemicals and bacteria that are consistently seen on or around a single person, but that vary between people. Many environmental aspects contribute to this microscopic amalgam — pets, household chemicals, flowers in bloom and even rain.

"The bottom line is that we all have our own microbiome cloud that we're schlepping around and spewing out," Snyder said.

Specific and unique signatures were captured for every individual (although Snyder added that DEET, an insect repellant, along with several carcinogens were found in just about every chemical sample). For example, the resident from San Francisco showed high rates of "sludge bacteria," or bacteria typically found in wastewater and sewage treatments. Snyder had consistently high fungal exposures at home due to what he suspects is the use of "green" paint. "The guy who painted my house was a really environmentally friendly, green person. And he avoided using paints with a substance called pyridine in it," Snyder said. Pyridine, which used to be a popular additive to house paints, has an inverse relationship with fungus, meaning the less pyridine, the more fungus.

Snyder's profile was the most diverse, as he took the device everywhere he went, both nationally and internationally, for two years, swapping out its filters for every new location. Outside his pet exposures (Snyder has a cat, a dog and a guinea pig), his signature also showed evidence of eucalyptus in the early spring months, providing some nuanced information about what might be causing his April allergies.

Connecting it to human health

Besides the four highly controlled participants, a dozen participants were added during different times of the year, helping Snyder capture exposures brought by weather, seasons and location.

"There are a lot of findings that haven't been described before — all kinds of fungal, bacterial and plant seasonal patterns," Snyder said.

Although the devices picked up potential pathogenic viral and bacterial sequences, it can be tricky to distinguish a threatening pathogen to humans from one of its harmless close cousins, he said.

As for the carcinogens, it's also more complicated than simply detecting them in the device. "We're measuring individual exposures, not absolute levels," he said. "So at this point the data isn't generalizable enough to make broad claims."

But that's not to say that one day it won't be. Snyder said that this study is just scratching the surface of human exposome data and how it relates to health, and his team's future goals center on better understanding the exposome as it relates to human health. "We want to measure more people in more diverse environments," Snyder said. "We also want to simplify the technology, ideally to the point that everyone can be out there measuring their own personal exposures — perhaps something like an exposome-detecting smartwatch."

The other Stanford author of the study is postdoctoral scholar Qing Liu, PhD.

Snyder is a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Stanford Children Health Research Institute, the Stanford Cancer Institute and the Stanford Neurosciences Institute.

The study was supported by funding from National Institutes of Health and a Stanford Spectrum population health pilot grant.

Stanford's Department of Genetics also supported the work. ISM

Concussion

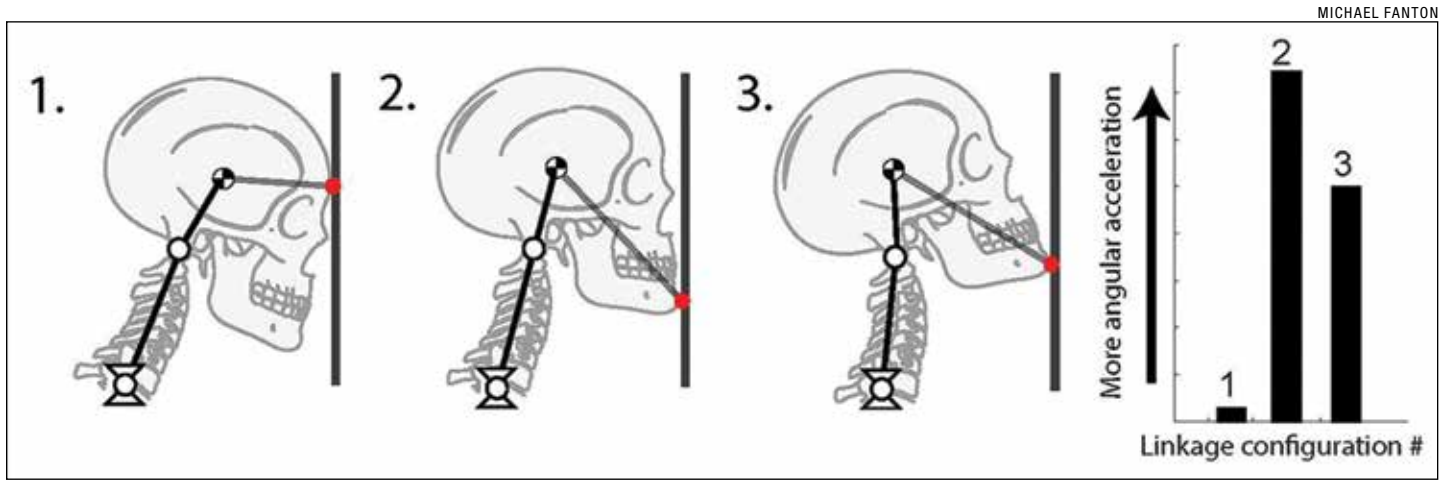
continued from page 4

your neck muscles could affect head acceleration and we wanted to figure out if that offered another strategy for reducing brain injury," Fanton said. "It was surprising that in these shorter-duration impacts, the neck muscles are not doing a whole lot."

The researchers were also curious whether head and neck positioning could alter front-to-back acceleration after a hard, fast hit. They ran their simulations with the head positioned at a variety of angles and found that small variations in position could mean the difference between high and low concussion risk. Their results showed that both the angle of the head and where it is hit affect the subsequent rotation of the head.

All this raised the question of how woodpeckers are able to withstand so much pounding — thought to produce head-on accelerations 10 times greater than those that cause severe concussions in athletes. So, the researchers created a simplified head and neck model of a woodpecker and ran it through the same positioning tests they had run in the human simulations. What they found is that small changes in position could substantially change the head acceleration the bird experienced. When the researchers aligned their model in the way real woodpeckers hold themselves as they peck, they noticed very low rotational acceleration.

MICHAEL FANTON



Three of the head and neck alignments modeled by the researchers (with hits simulated at the red dot) show how small differences affect angular acceleration, also called rotational acceleration. Greater angular acceleration increases the likelihood of concussion.

However, the group cautioned that position alone likely doesn't explain the woodpecker's ability to withstand these forces. Scientists have suggested the size of their brains and features of their beak may be mitigating factors.

Focusing on prevention

Although the Camarillo lab and others in the field are finding that the neck muscles and ligaments might not prevent the kinds of head movement that lead to concussions, neck positioning is not a simple solution. Positions that could prevent concussions might make people more susceptible to other injuries, such as paralysis, and what protects one person could potentially raise the injury risk of another person involved in the same impact.

"Discovering how sensitive the head is to slight changes in positioning has implications on design of helmets and other protective equipment," Camarillo said. "For example, could the facemask in football be offering a lever arm that adds to the rotation of the head and therefore risk of concussion? Are downhill mountain bike helmets protecting the chin at the cost of the brain? We hope to use this model we have developed to determine better design geometry of helmets and potentially for input to coaching on how to brace for impact."

Ultimately, Camarillo is hoping this kind of modeling work can aid in developing better ways of preventing head injuries.

Other Stanford co-authors are former graduate students Calvin Kuo, PhD, and Fidel Hernandez, PhD; and graduate student Jake Sganga.

Camarillo is a member of Stanford Bio-X, the Stanford Child Health Research Institute and the Stanford Neurosciences Institute.

This research was funded by the Stanford Child Health Research Institute, Stanford Bio-X, the Office of Naval Research and the National Science Foundation.

The Department of Bioengineering, which is jointly managed by the schools of Medicine and of Engineering, also supported the work. ISM

■ OBITUARY

Luigi Luca Cavalli-Sforza, a giant in population genetics, dies at 96

By Amy Adams

Luigi Luca Cavalli-Sforza, MD, professor emeritus of genetics at the School of Medicine, died Aug. 31 of natural causes in his home in Belluno, Italy. He was 96.

Cavalli-Sforza was among the first to use genetics to track human migration patterns. His blend of anthropology and genetics led to a new field he called genetic geography, in which he followed the spread of genetic variations to track how humans populated the world.

"Luca was one of the first scientists to use genetic information to understand the relationships between different human populations at the level of the DNA," said Marcus Feldman, PhD, professor of biology at Stanford. "He was always ahead of the game. Luca wasn't a follower; he was a pioneer in the true sense of the word. If other people were doing it, he didn't want to touch it."

A native of Italy

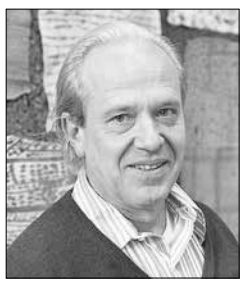
Born in Genoa, Italy, in 1922, Cavalli-Sforza earned his MD from the University of Pavia in 1944 and worked there as a physician for a year before becoming a genetics professor, teaching at Cambridge, Parma and Pavia. Although he began his genetics career studying microbiology, he quickly became interested in human genetics.

By the time Cavalli-Sforza arrived at Stanford in 1970, he had already begun developing new statistical tools for analyzing molecular differences between groups of people around the world. His earliest work involved looking at how the A, B and O blood types were represented in populations. From that, he devised the first of his many maps depicting human variation across the globe.

As technology became available to survey variations at the genetic level, Cavalli-Sforza began examining genetic changes on the Y chromosome in populations around the world. This chromosome is passed directly from father to son, preserving a clear paternal lineage. Using this technique, he traced the male lineage back to a single male ancestor, dubbed "Adam," living roughly 70,000-100,000 years ago in sub-Saharan Africa.

According to Cavalli-Sforza's data, Adam's sons stayed close to home for about 23,000 years. At that time, small bands packed up and headed north to Europe, Asia and Australia. Years later, a second and third wave of travelers wandered off, some overlapping with past migrations and others staking out new territory.

These migration patterns have since been confirmed by researchers using different combinations of genetic markers. "Different genes have different histories. But when several genes are telling the same story, you're more confident that you've got the history right," said Cavalli-Sforza's longtime Stanford collaborator Peter Underhill, PhD, senior research scientist in genetics, in *Stanford Medicine* magazine.



Luigi Luca Cavalli-Sforza

Cavalli-Sforza's genetic work earned him accolades from those hoping to break down the barriers of race. He found that people from the same population are as genetically diverse as people from two different groups, essentially showing that at the genetic level, there is no such thing as race. Reviewing Cavalli-Sforza's 2000 book *Genes, Peoples, and Languages* in *The New York Review of Books*, Jared Diamond praised the Stanford researcher for "demolishing scientists' attempts to classify human populations into races in the same way that they classify birds and other species into races."

Parsing the journey of humankind

In an attempt to extend his genetic analysis of people, Cavalli-Sforza began the Human Genome Diversity Project to gather and store genetic samples from populations around the world. Although Cavalli-Sforza and others saw the project as a way to safeguard DNA from dwindling populations and to learn about human history, others saw it differently. He was accused of biopiracy, exploitation and of enabling biological weapons that could attack the genetics of particular ethnic groups. In the end, the group collected samples from more than 50 populations that are now stored at the Center for the Study of Human Polymorphisms in Paris.

"The HGDP was a huge contribution. It was really one of the first projects to create a comprehensive view of worldwide genetic diversity," said Jonathan Pritchard, PhD, professor of genetics and of biology at Stanford and a longtime collaborator of Cavalli-Sforza's. "Since then, many large international projects have built on that idea, recapitulating aspects of HGDP — but the fundamental idea came from Luca."

Based on those samples, a Stanford research group, including Cavalli-Sforza, published a 2008 *Science* paper providing a detailed look at human genetic diversity. What they found backed up much of what Cavalli-Sforza had learned from more than 40 years of studying blood groups, the Y chromosome and collections of genetic markers: People can't be divided into racial groups based on DNA.

"It was a watershed paper and, in many ways, a vindication of Luca's work," Feldman said. "There's no doubt that paper stimulated and set up the whole field of DNA population genetics, and Luca was really the father of that field."

Despite the prevailing scientific interpretation that his work demolished the idea of race, Cavalli-Sforza's findings remained controversial. White supremacists have argued that because genetic variations are associated with particular geographical locations, that's as good as providing a genetic basis for race, an argument that Cavalli-Sforza rejected.

Cataloging human variation

Not all of Cavalli-Sforza's findings were so contentious. He and Feldman founded the field of cultural evolution, a theory that social change resembles a Darwinian evolutionary process. Among the mysteries addressed by their work was the question of how agriculture spread. Archeologists had learned that the trappings of agriculture traveled at the rate of about 1 kilometer per year. What they didn't know is how those artifacts had spread. Did stationary populations disperse agriculture by word of mouth, or did new agricultural groups migrate, taking their new knowledge with them? Cavalli-Sforza led work that revealed the new farmers had slowly migrated into hunter-gatherer territories, likely through intermarriage.

The genetic topography maps Cavalli-Sforza produced also helped clarify the factors that were most important in influencing gene frequencies within a population. These include natural selection, migration, mutation and drift. Although all factors play a role in determining what genetic traits become common in a given population, random chance turns out to be a major driving force in human history. Among the most important random events is the bottleneck effect, in which a small group of people containing an uncommon trait populate an area. Because of the genetic makeup of the founders, that trait becomes common in the new population despite carrying no evolutionary advantage.

Based on his lifetime of work, Cavalli-Sforza wrote what is considered a landmark description of human genetic variation. Originally published in 1994, *The History and Geography of Human Genes* is a 1,000-page tome of genetic information about human history.

"He's one of the greatest minds I've ever come across," said Feldman, who is also the Burnet C. and Mildred Finley Wohlford Professor at Stanford. "He had such a breadth of interest and depth of knowledge in so many fields. When I was a young assistant professor, whenever I was around Luca, it was like opening your eyes to a world of scientific possibilities."

Cavalli-Sforza's life's work culminated with a call to analyze the world's populations in even finer genetic detail. The information about human history that comes from these studies will be built on the research of Cavalli-Sforza, who pioneered the idea that we can learn about our past through our DNA.

He is survived by his sons Matteo, Francesco and Luca Tommaso Cavalli-Sforza, and by his daughter Violetta Cavalli-Sforza.

Hanae Armitage contributed to this report.

ISM

Leaders

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was born with a rare genetic disease —NGLY1 deficiency — which only 36 other people are known to have, and which is associated with movement disorders, delayed growth, seizures and liver problems. Wilsey told the audience how, after physicians at Lucile Packard Children's Hospital Stanford had helped to diagnose their daughter's illness, he and his wife, Kristen, partnered with their daughter's physicians and others at Stanford Medicine and around the world to initiate a model for biomedical research into rare genetic diseases. Wilsey praised the collaborative spirit of the Stanford Medicine team he worked with to identify his daughter's disease.

"The team at Stanford was definitely ahead of the wave on this receptivity in working together with patients," he said.

Enwistle asked Wilsey what advice he had for clinicians and scientists in the room. "We often hear, 'Well, this is how it's done,'" Wilsey said. "And if it was done so well before, we'd have a lot more breakthroughs and cures. So, fight that mantra of 'this is how it's done.' Push people and challenge that, and try to find new solutions."

Progress, priorities and challenges

In a panel discussion moderated by Leslee Subak, MD, professor and chair of obstetrics and gynecology, Minor, Entwistle and Lund discussed a variety of topics that detailed Stanford Medicine's progress, including both the opening of the new main building for Lucile Packard Children's Hospital at the end of 2017 and the opening of the new Stanford Hospital, which, Entwistle said, is just 14 months away. "This will be the most technologically sophisticated hospital in the world," he said.

They also discussed challenges, such as finding workspace for researchers. "No matter what metric we look at — research dollars per square foot of research space, productivity of individual faculty members — our faculty are incredibly productive given the space constraints under which our faculty operate," Minor said. He described two new 200,000-square-foot buildings under construction: the Biomedical Innovation Building, devoted to "wet lab" research; and the Center for Academic Medicine, which will contain offices for faculty and clinical trial coordinators, as well as dry labs. The buildings are scheduled to open in 2020.

> "This will be the most technologically sophisticated hospital in the world."

Subak asked the leaders to talk about their progress in diversity and inclusion, which the dean emphasized as a top priority for the School of Medicine. "I'm pleased that today both our MD and our PhD programs have roughly doubled the representation from groups who are underrepresented in medicine as compared with six years ago," Minor said. "On the faculty side, we're making sure we are constantly, as a leadership team, promoting inclusion among our community."

Among Stanford Medicine's challenges, the upcoming November ballot measures — Measure U in Livermore and Measure F in Palo Alto, both of which would give local city administrators the authority to cap, regulate and enforce health care costs — are among the most pressing. Entwistle detailed the background of the ballot initiative, noting that not only is Stanford Medicine "firmly against the ballot initiatives," but so, too, is the local government. Entwistle noted that the Palo Alto City Council "voted unanimously 9-0 to oppose this."

Subak encouraged everyone to get out and vote on Nov. 6.

Wrapping up the event, Minor introduced a video that provided a look at the many ways Stanford's precision health vision is now a reality, with the promise to touch 2 billion lives worldwide by 2025. For example, Stanford Medicine physicians have developed an emergency services system in India that so far has served 800,000 people, and free hepatitis B vaccinations and prevention projects at the Asian Liver Center at Stanford have reached 450,000 pregnant women, among many other collaborative efforts globally and locally.

Outside Berg Hall, both before and after the event, audience members mingled and visited several kiosks showcasing advances at Stanford Medicine, such as the Virtual Heart, which allows people to don a virtual reality headset and experience the human heart in 3-D, and Project Baseline, a multiyear project with Verily (an Alphabet company) and Duke University to gather human health data and build a model for disease prevention. One kiosk was dedicated to showcasing faculty, staff and students' proudest moments, which were penned on sticky notes and displayed together in a show of colorful, collective pride. ISM

Curriculum

continued from page 1

complete an MD-PhD program. The redesign committees also sought to make the curriculum more flexible, re-engage basic scientists in teaching, continuously improve the quality of teaching across the board, and foster scientific investigation while maintaining students' clinical training and preparation for residency.

"Students come to Stanford knowing about its prestige in investigation and discovery," said Paul Berg, PhD, professor emeritus of biochemistry and a co-recipient of the 1980 Nobel Prize in chemistry, who played a major role in shaping and championing the new curriculum. "We want to instill that same culture into the medical students. And my own experience is: Any success early hooks you. You get somebody who makes an interesting discovery, writes an interesting paper and gets it published — that sticks."

Quality research is longitudinal

While Stanford has long required a single quarter of scientific research as part of the criteria for medical students to graduate, the previous curriculum did not allow flexibility for longer research projects. Students who engaged in long-term projects typically took a full year off to complete them, disengaging from their classmates and coursework. Daniel Bernstein, MD, professor of pediatric cardiology and associate dean for curriculum and scholarship, noted that quality scholarship "often depends on an experience that's longitudinal."

Typically 75-85 percent of medical students at Stanford have opted for at least one extra year of medical school to incorporate additional scholarly pursuits, Bernstein said. "When I arrived at Stanford over 30 years ago, this approach was unique among medical schools, and today it still is unique," he said.

Students who choose the MD-PhD program, also known as the Medical Scientist Training Program, spend their first two years in medical education before starting full-time laboratory research. After three to five years of research, they complete and defend their PhD thesis before finishing their the last two years of medical training, which are dedicated to clinical rotations. Stanford MD-PhD students are fully supported through the entire program by a combination of funding from an NIH training grant, individual graduate programs and School of Medicine funds.

"Our students have always been keen to do research," said Neil Gesundheit, MD, MPH, professor of endocrinology and senior associate dean for medical education. "The dream of each student is, in the process of research, to come up with a discovery that has the potential to change practice, be innovative and improve people's lives."

Envisioned by Nobel laureates

The Discovery Curriculum began as the vision of a small team of faculty that included Utz and Berg, along with Brian Kobilka, MD, the Hélène Irwin Fagan Chair in Cardiology, professor of molecular and cellular physiology and co-recipient of the 2012 Nobel Prize in chemistry. Participating in the early stages of the curriculum's development were Russ Altman, MD, PhD, the Kenneth Fong Professor and professor of bioengineering, of genetics, of medicine and of biomedical data science; Andrew Fire, PhD, the George D. Smith Professor in Molecular and Genetic Medicine, professor of pathology and of genetics and co-recipient of the 2006 Nobel Prize in physiology or medicine; and Donald Regula, MD, professor of pathology.

"The curriculum had been very inflexible," Kobilka said. "And I noticed that students rarely came to my lab to ask about doing some basic research as part of their experience."

Kobilka also noticed that Stanford Medicine's basic scientists had gradually become less involved in teaching, and that troubled him. "Stanford is a special place," he said. "It's a place where students can have access to cutting-edge research when they're in medical school, partly because it's a great university and also because the basic science departments in the medical school and undergraduate campus are all contained in a very small geographic footprint. The inflexible curriculum made it difficult for students to take advantage of all that Stanford had to offer."

The group also noted that an increasing number of medical schools were moving to reduce the time necessary to complete their medical degree programs from the traditional four years down to three in response to a growing shortage of clinicians — a shortfall projected by the Association of American Medical Colleges to reach 100,000 by 2030. But the Stanford group believed that, for a research-intensive medical school like Stanford, it was urgent to do the opposite: reaffirm Stanford's commitment to scholarship and discovery and create a pathway for physician-scientists that would be an alternate to the MD-PhD, which takes longer, costs universities more and often draws graduates away from clinical work entirely into laboratory research.

> "The opportunities for dual training for interdisciplinary work are enormous."

"At Stanford, we pride ourselves on being the most research-intensive medical school in the world," said Utz, who graduated from the School of Medicine in 1991. "To advance medicine, scholarship is essential."

New curriculum takes shape

The group's early conversations took shape as Gesundheit and two administrative committees championed by the dean aided the effort to formalize a plan, leading to the first major overhaul of the curriculum in 15 years.

"From our earliest conversations, Dean Minor was focused on the future possibilities of a new curriculum," Utz said. "He could see the need for a uniquely Stanford balance between scientific investigation and superlative clinical training, and helped to ensure it became a reality."

Preetha Basaviah, MD, clinical professor of medicine and assistant dean for pre-clerkship education, and Bernstein co-chair the committee charged with implementing the Discovery Curriculum. Basaviah spent a decade as one of the directors of the Practice of Medicine course, which began in 2003 and now makes up about 40 percent of the medical student curriculum. "Preparing students for clinical care is a top priority of the School of Medicine," Basaviah said. "We've kept a continued focus on clinical excellence with longitudinal mentorship that includes advancing communication and clinical skills as well as professionalism."

A few of the new classes in the Discovery Curriculum began during the 2017-18 academic year. Now, the curriculum is fully implemented. It includes several restructured courses and some entirely new ones, along with an option to split the second year of medical school into two years to give students large blocks of free time for research during the second and third years of school.

Among the new courses is the Pharmacologic Treatment of Disease, led by Kobilka. His participation, not only as a designer of the curriculum but as one of its teachers, is notable. "Usually Nobel Prize winners are off doing other things and not teaching in medical schools," Utz said. "But ours are here on campus. They're vocal. They're in front of the students and deeply involved."

STEVE FISCH

(From left) Medical students Isaac Jackson, Jenny Tiskus, William Shi, Joshua Guild, Areli Valencia and Justin Jia are among the students who chose to split their their second-year coursework into two years, an option now available as part of the new curriculum.

Time, and funding, for discovery

Not all students will choose to split their second-year coursework over two years. But those who do will have a variety of options for using the unscheduled time, and will pay the same tuition for five years that they would have for four.

Berg said that although some will choose to do research, many of the MD students he interviewed during the redesign efforts expressed a wish to take classes on the university's main campus and possibly earn a master's degree. Other students may opt to split the curriculum for other purposes — parenting a new baby, training for the Olympics, writing a novel or just slowing down the pace of learning. The advantage of the split curriculum is that students can start a research project during the spring or summer quarter of their first year and have sufficient time to continue it for the next two years. This type of extended scholarly experience had not been possible in the previous curriculum.

STEVE FISCH

Laura Bachrach co-teaches the endocrine module of the Science of Medicine course, which was modified for the new Discovery Curriculum.

"We are luckily a medical school in the middle of a major university campus," Gesundheit said. "The opportunities for dual training for interdisciplinary work are enormous."

Opportunities for financial support are available to students who add a sixth year to earn a newly offered master's degree in biomedical investigation. A new $2.5 million grant from the Burroughs Wellcome Fund and other funding sources could pay for that additional full year of research, as well as the two years of clinical rotations, for up to five students each year.

"The six years spent in completing the MD-MS training is shorter and less costly than the seven to eight years used to obtain the MD-PhD. Those two features increase the likelihood the student will elect an investigative career," Berg said.

'Feasible and worthwhile'

Students who began medical school in the fall of 2017 — and who are now starting their second year — are the first to have the option to split their second-year coursework into two years.

"I jumped at this opportunity," said Joshua Guild, a second-year student who is researching how alveoli — the tiny air sacs that serve as the site of gas exchange in the lungs — are repaired by stem cells after injury. "The faculty here have done an amazing job of introducing additional flexibility in the curriculum to make an opportunity such as this both feasible and worthwhile."

Guild's classmate, William Shi, sees the chance to split his second year as a "sneak preview" into his future career as a physician-scientist. "I plan to spend this time conducting research, working to advocate for my classmates and patients, and taking care of my personal wellness," he said.

Students who are the first to take part in the Discovery Curriculum know that their feedback will be an important part of refining and perfecting the new program. "I'm apprehensive about being the first cohort to split the curriculum," said second-year student Areli Valencia, who is using the extra time to work toward a master's in bioinformatics and continue his research. "But I'm also excited because I'm able to design my own path."

For students, embarking on such a novel curriculum may feel like a big change, but innovation is precisely the point. "We're persuading students to do the unusual, to be the pioneers," Berg said. "We built it, now we want people to come and be a part of it."

Students can still opt for the traditional four-year clinical MD degree at Stanford, but for those looking to change the face of medicine, from discovering new treatments to designing better health care systems, the Discovery Curriculum provides a foundation and pathway.

"What we want our students to do is not to emulate us," Gesundheit said, "but to eclipse us. We want them to gain skills and leadership, knowledge — whatever they need — to become the academicians and the thought leaders, the change agents for the future." **ISM**

OF NOTE

reports on significant honors and awards for faculty, staff and students


Marcella Alsan


Harris Carmichael


Stacie Vilendrer


E.J. Chichilnisky


Valerie Chock


Nancy Dudley


Aaron Gitler


Gerald Grant


Michael Greicius


Geoffrey Gurtner

MARCELLA ALSAN, MD, PhD, was promoted to associate professor of medicine, effective July 1. Her research explores the relationship between health and economic development, with a focus on infectious disease. She is also working to identify causes and potential solutions to health disparities in the United States and abroad.

HARRIS CARMICHAEL, MD, and **STACIE VILENDRER**, MD, MBA, both clinical instructors of primary care, have received the Stanford/Intermountain Fellowship in Population Health, Delivery Science and Primary Care. The two-year fellowship, which began in July in partnership with the Intermountain Healthcare Delivery Institute, was created to support the education and training of the next generation of leaders in population health, primary care and care-delivery science.

E.J. CHICHILNISKY, PhD, the John R. Adler Professor and professor of neurosurgery and of ophthalmology, received an inaugural research traineeship award from the National Science Foundation. The five-year, $3 million award will support graduate education aimed at accelerating fundamental developments in neuroscience by attracting and training young researchers from technical disciplines such as engineering and physics.

VALERIE CHOCK, MD, was appointed associate professor of pediatrics, effective June 1. Her research uses techniques such as near-infrared spectroscopy to study brain injury and development in critically ill babies, premature infants and infants with congenital heart disease.

NANCY DUDLEY, PhD, MSN, was awarded the inaugural postdoctoral fellowship in nursing science in the Department of Medicine Division of Primary Care and Population Health-Palliative Care Section. The fellowship is funded by the Stanford Nurse Alumnae. Her research will focus on palliative care in ambulatory settings at Stanford.

AARON GITLER, PhD, professor of genetics, was selected as one of six new Innovation Fund investigators by the Pew Charitable Trusts. The fund awards grants to collaborative pairs of Pew scholar alumni. This two-year, $200,000 grant will support the design of protein-targeting therapies for the fatal motor neuron disease amyotrophic lateral sclerosis. Gitler's collaborator is Michael Rape, a professor of molecular and cellular biology at UC-Berkeley.

GERALD GRANT, MD, was promoted to professor of neurosurgery, effective June 1. He specializes in treating children with brain tumors and intractable epilepsy using brain mapping techniques and awake language mapping. His research focuses on understanding the blood-brain barrier in order to enhance drug delivery to brain tumors in children.

MICHAEL GREICIUS, MD, MPH, associate professor of neurology, received a five-year, $3.4 million R01 grant from the National Institutes of Health to lead a multicenter study of whole-genome sequencing in extreme phenotypes of Alzheimer's disease. The study will seek rare, causal genetic variants in patients who have early-onset Alzheimer's despite not having the high-risk APOE4 gene, as well as rare, protective genetic variants in healthy older control patients who have one or two copies of the APOE4 gene but do not have dementia.

GEOFFREY GURTNER, MD, the Johnson & Johnson Distinguished Professor in Surgery II, has been awarded a U01 grant from the National Institute of Diabetes and Digestive and Kidney Diseases. The four-year, $1.73 million grant will support efforts at the Stanford Advanced Wound Care Center Clinical Research Unit to validate biomarkers for diabetic foot ulcers that can predict healing outcomes, guide treatment, and monitor healing and response to treatment. Gurtner also was appointed chair of the National Institutes of Health Diabetic Foot Consortium.

WAN HONG, MD, a resident in general surgery, was awarded a T32 training grant from the National Institutes of Health. The one-year, $49,000 grant will support her study of immunotherapy in solid tumors.


Wan Hong


Michael Ma


Vinod Menon


Claudia Mueller

MICHAEL MA, MD, was appointed assistant professor of cardiothoracic surgery, effective July 1. His research focuses on understanding and treating congenital heart and lung conditions for pediatric patients.

VINOD MENON, PhD, the Rachael L. and Walter F. Nichols, MD, Professor and professor of psychiatry and behavioral sciences, received the Method to Extend Research in Time award from the National Institutes of Health. The award is presented to investigators who have demonstrated superior research competence and productivity. It will provide $3.86 million over five years to support his research investigating neurocognitive longitudinal trajectories and outcomes in mathematical learning disabilities.

CLAUDIA MUELLER, MD, was promoted to associate professor of surgery, effective July 1. Her research interests include physician well-being and performance, and the relationship between children's beliefs about their health and their responses to illness.

SERGIU PASCA, MD, PhD, assistant professor of psychiatry and behavioral sciences, received the 2018 Early Career Life Science Award from the American Society of Cell Biology. The award recognizes an outstanding scientist who has served as an independent investigator for no more than seven years and has made important contributions to cell biology.

JEAN TANG, MD, PhD, was promoted to professor of dermatology, effective June 1. Her clinical research focuses on developing gene therapies for genetic skin diseases, such as basal-cell nevus syndrome and epidermolysis bullosa. She also studies new ways to treat and prevent melanoma and nonmelanoma skin cancer, and the relationship between sun protection and vitamin D.

DERRICK WAN, MD, associate professor of plastic and reconstructive surgery, has been awarded an R01 grant from the National Institutes of Health. The five-year, $1.25 million grant will allow his team to explore irradiated head and neck cancer soft-tissue reconstruction using fat transfer.

MARIUS WERNIG, MD, PhD, associate professor of pathology, was awarded the 2018 Ogawa-Yamanaka Stem Cell Prize by the Gladstone Institutes, a nonprofit biomedical research organization. The $150,000 prize recognizes individuals whose original translational research has advanced cellular reprogramming technology for regenerative medicine.

GREG ZAHARCHUK, MD, PhD, was promoted to professor of radiology, effective June 1. His research focuses on developing new MRI and positron emission tomography techniques to better understand human brain function, delineate brain structures and diagnose brain diseases. He also uses artificial intelligence to improve the quality and safety of medical imaging. **ISM**


Sergiu Pasca


Jean Tang


Derrick Wan


Marius Wernig


Greg Zaharchuk

Awards for promise in biomedical research, clinical care

Four School of Medicine clinician-scientists have been awarded the Doris Duke Charitable Foundation 2018 Clinical Scientist Development Award.

The early-career researchers were among 18 selected for the award based on the rigor of their research and their commitment to excellence. Each researcher will receive a total of $495,000 over three years.

The Stanford recipients are:

BRICE GAUDILLIERE, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine, who is using mass spectrometry to investigate how the human immune system senses the onset of labor in normal and preterm pregnancies.

CHRISTIN KUO, MD, assistant professor of pediatrics, who is investigating pulmonary neuroendocrine cell signaling in the developing lung and in disease.

CAROLYN LEE, MD, PhD, assistant professor of dermatology, who is studying the regulation of skin cancer progression.

KEVIN WANG, MD, PhD, assistant professor of dermatology, who aims to improve the treatment of skin disorders by manipulating the three-dimensional chromosomal architecture to control gene expression in wound healing and tissue regeneration.

Diversity, science leadership awards for student-faculty pairs

Two graduate students at the School of Medicine and their faculty advisers have been awarded fellowship grants by the Howard Hughes Medical Institute.

The institute awarded 45 Gilliam Fellowships for Advanced Study grants to student-adviser pairs who have the potential to become leaders in their respective fields and are dedicated to promoting diversity in the sciences.

Each pair will receive an annual award of $50,000 for up to three years, including a stipend, a training allowance and an institutional allowance. The Stanford student-adviser awardees are:

MATIAS KAPLAN, a bioengineering graduate student whose work focuses on understanding the relationship between sequence and structure of certain RNA switches for use in metabolic engineering and medical applications. His adviser is **CHRISTINA SMOLKE**, PhD, professor of bioengineering.

ABEL FERREL, a microbiology and immunology graduate student whose work focuses on how the single-celled Toxoplasma parasite interacts with the host cell in the chronic stage of infection. His adviser is **JOHN BOOTHROYD**, PhD, the Burt and Marion Avery Professor and professor of microbiology and immunology. **ISM**