INSIDE STANFORD MEDICINE

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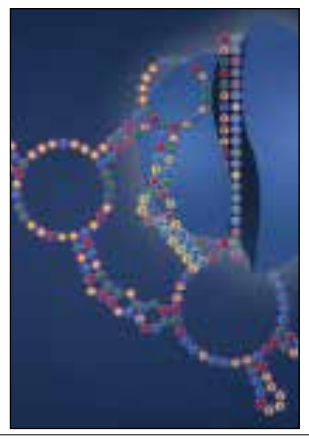

A new online game challenges players to design an on/off switch for the gene-editing tool CRISPR.

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New medical students slip into white coats

By Tracie White

STEVE FISCH

First-year medical students gather on a balcony at the Li Ka Shing Center for Learning and Knowledge on Aug. 25 following the stethoscope ceremony.

When the staff at the School of Medicine's Office of MD Admissions began to review the thousands of applications they received last fall, they were not only looking for applicants who excelled academically, but also for those who best reflected the school's mission of promoting leadership, innovation, discovery and diversity.

This is according to Iris Gibbs, MD, associate dean for MD admissions, who pointed to Bongeka Zuma as an example of one such person. Now among the 100 new students who began classes on Aug. 28, Zuma was the valedictorian of the inaugural class of Oprah Winfrey's Leadership Academy for Girls in South Africa. She was raised in poverty in the province of Kwa Zulu-Natal, where she said every Saturday there was a funeral, and family and friends routinely died of preventable diseases.

"I was really attracted to Stanford because I wanted a school that stressed that I could be a doctor and also have the opportunities to be something else," said Zuma, who never saw a physician as a child. "I hope to make changes in health care by getting involved in policy in government back home."

Gibbs said Zuma is the type of student Stanford seeks: One with the potential to shine in the classroom and the clinic, as well as with the qualities of a future leader in health care.

Multifaceted backgrounds

"Everyone is struck by Bongeka's story," said Gibbs, who is also a professor of radiation oncology. "And when you meet her she has this wonderful confidence and sense of giving back.

"All of our students exhibit a similar multifaceted background," Gibbs added.

The first-year medical students bring with them a wide variety of life experiences. There's an Olympic gold medalist, the founder of a green technology company, a former DREAMer who came to the United States as an undocumented immigrant, and an accomplished classical pianist. Sixteen were varsity athletes, including Owen Marecic, a retired NFL player and former Stanford football player who currently works in a research lab on campus. Five of the students were Fulbright fellows, two were Rhodes scholars and 18 hold advanced degrees. Twenty-six are racial and ethnic minorities underrepresented in medicine, including 11 African-Americans and 12 Latinos.

Lloyd Minor, MD, dean of the School of Medicine, noted this as he welcomed the new medical students on Aug. 25 during a ceremony at which they were given white coats and stethoscopes. The stethoscopes, symbolizing the close relationship between physician and patient, were provided by Stanford Medicine Alumni Association.

"You come from all around the globe with various perspectives and experiences," Minor said. "You've played the bagpipes, run companies, tap danced, written poems, published groundbreaking scholarship, competed in the NFL and the Olympics, and made a lasting impact on underserved communities and our natural environment. I'm honored that you're bringing your intellectual rigor, generosity and unbridled creativity to this campus and to our community, and that you chose Stanford as the place to begin your journey in medicine and in life."

Furthering the school's goals

It was Minor who helped to articulate the school's mission to embrace inclusivity and diversity when he first arrived at Stanford as dean in 2012, said Gibbs, who was a member of the admissions committee at See STUDENTS, page 4

Trying to hack fear with virtual reality

By Bruce Goldman

I stood, exposed, at the prow of an underwater vessel and watched a great white shark come toward me, its rows of gleaming, pointy teeth headed for my throat.

The shark got within about 2 feet of me, hung a U-turn and smoothly swam away. Another approached. I was stuck in the middle of a whole school of them.

A guilty source of comfort was the knowledge that a couple of the other divers were way more exposed than I was. I wouldn't want to be in their fins.

Most calming of all, I knew that none of this was real — or, at least, the conscious part of my brain did. Had I been convinced I was really 100 feet underwater and surrounded by these bionic buzz saws, my fear levels would have been registering on the Richter scale. I would be freaking out.

BRIAN SMALE

Andrew Huberman wants to learn more about fear by identifying the neural circuitry underlying it, and pinpointing the circuits' settings during episodes of fear.

In actual fact I was standing in a small room immersed in sensory inputs, mostly visual, telling me that I was below the surface of the waters off Guadalupe — an island 150 miles west of Baja California — dodging the serial swim-bys of a few dozen great white sharks.

Vision's role in fear

Andrew Huberman, PhD, an associate professor of neurobiology at Stanford, doesn't know the meaning of fear — literally. You probably don't, either, although we all know it when we feel it: Our heartbeat speeds up, our limbs tingle, our breathing becomes shallow and rapid, our muscles pulse with multiples of their normal strength and See FEAR, page 6

Fathers of U.S. newborns getting older, study finds

By Bruce Goldman

STEVE FISCH

Michael Eisenberg is the senior author of a study on the age of newborns' dads in the United States.

The average age of newborns' fathers in the United States has grown by 3.5 years over the past four decades, according to a new study from investigators at the School of Medicine.

Men over the age of 40 now account for about 9 percent of all U.S. births. Men over the age of 50 account for nearly 1 percent.

Those statistics come from the Stanford study, which is the first comprehensive analysis of all live births reported to a federal data depository in the United States from 1972-2015: to be precise, 168,867,480 births.

The researchers obtained the data from the National Vital Statistics System, an intergovernmental data-sharing program sponsored by the federal Centers for Disease Control and Prevention. See FATHERS, page 7

Children's hospital uses virtual reality to help young patients cope

By Kate DeTrempe

As patients at Lucile Packard Children's Hospital Stanford undergo routine medical procedures, they are being whisked away to swim under the sea, zap flying cheeseburgers in outer space, catch basketballs using their heads and fly on paper airplanes through the sky, thanks to virtual-reality technology, which is being implemented throughout the hospital to help ease patients' feelings of pain and anxiety.

Packard Children's is one of the first hospitals in the country to begin implementing distraction-based VR therapy within every patient unit.

"Many kids associate the hospital with things they deem stressful and scary," said pediatric anesthesiologist Sam Rodriguez, MD, co-founder of Packard Children's Childhood Anxiety Reduction through Innovation and Technology, or CHARIOT, program, which is leading the VR rollout. "We are finding that the ability to distract these patients with fully immersive, fun and relaxing sensory environments can have a significant impact on the anxiety and pain that they experience during minor procedures, dressing changes and other medical treatments."

In February, 9-year-old Blaine Baxter suffered a severe injury to his arm while racing a go-kart and had to undergo daily, painful dressing changes. "He would immediately start crying and scream out of fear, and had to be sedated before doctors could approach his arm," explained Blaine's mother, Tamara Baxter. "He was so riddled with anxiety after everything he had been and was going through. VR was a game changer for Blaine. As soon as he put the goggles on, sedation was no longer needed, and during his dressing changes we went from hearing pain-stricken screams to 'Wow, I'm under the sea looking at sea snakes. This is so cool. You have to see this!'"

Evolution of CHARIOT

The use of VR is a novel experience for many of the patients at Packard Children's, said Veronica Tuss, a child life specialist with the hospital's Child Life and Creative Arts Department. The department's members engage patients in age-appropriate activities to help normalize their time in the hospital. Through providing education and procedural support, they play a key role in helping to decrease patients' stress levels prior to procedures. "VR is often so unfamiliar that it is instantly engaging and incredibly distracting," Tuss says. "If I'm preparing a child for their very first IV, and they share with me that they don't want to see what's happening procedurally, I know I need a distraction that is visually engaging. With VR, an often-intimidating setting suddenly becomes this really cool thing or place that they get to explore. It can minimize the experience of getting the IV to the point that we may actually turn a negative experience into a positive one."

The hospitalwide VR rollout is the latest evolution in distraction-therapy techniques pioneered by Rodriguez and fellow anesthesiologist Thomas Caruso, MD, who co-founded CHARIOT with Rodriguez. In 2015, the duo introduced the Bedside Entertainment and Relaxation Theater, which uses video projection to allow patients undergoing surgery to watch movies, music videos and other entertainment on a large screen attached directly to their gurney up to the moment they enter the operating room.

Earlier this year, CHARIOT launched Sevo the Dragon, an interactive video game projected on the BERT screen that takes a necessary part of anesthesia — breathing anesthesia medicine through a mask — and transforms it into a game. While BERT is great for younger children, the VR experience is becoming a useful tool, especially for older children, said Rodriguez and Caruso, both of whom are clinical assistant professors of anesthesiology, perioperative and pain medicine at the School of Medicine. The VR goggles escalate the immersive entertainment experience to a 360-degree view of relaxing scenery and engaging games.

For patients as young as 6, VR distraction therapy is being used in Packard Children's Bass Center for Childhood Cancer and Blood Diseases, short stay unit and emergency department; the vascular access, imaging, ambulatory orthopedics and general surgery clinics; and the perioperative unit. It will be rolled out by the end of the year to the hospital's acute care floor units, Stanford Children's Health's ambulatory surgery clinics and even the labor and delivery unit. The goal is for all of the hospital's 29 child life specialists to be trained on the use of VR goggles by that time. In addition, pediatricians at the Stanford Children's Health Bayside Medical Group-Berkeley clinic will be implementing VR technology during immunizations for patients who are fearful of needles.

"Children shouldn't grow up being afraid to go to the doctor to have a shot, but certain experiences can cause phobias that last into adulthood. Needle phobia is a common example of that, and it's the primary reason adults avoid important immunizations like flu shots," Caruso said. "Now, when patients get a shot while they are wearing VR goggles, they are reporting only limited levels of pain, if any."

Customizing VR for the hospital

The CHARIOT team has medically customized the VR headsets to better fit kid-sized heads with an easy-to-clean strap and a disposable screen liner for immunocompromised patients. Sound capabilities allow the volume to be adjusted so the care team can communicate with patients during procedures, and each headset is accompanied by a smartphone preloaded with customized content specific to children in the hospital.

The CHARIOT team works carefully to select games that require limited head and arm movement so kids seated in bed can play without turning their bodies or getting tangled in IV lines and other wires, and so patients with arm bandages or casts can still participate. CHARIOT also works with companies to adapt commercially available games for the health care setting, removing themes of injury or death and eliminating "game over" termination so that the distraction of the game doesn't go away at the moment patients need it the most.

Working with Silicon Valley-based software engineers, Rodriguez and Caruso are also developing original VR content specifically created for the pediatric patient population. Their first game, Spaceburgers, was developed with Juno VR and is specifically designed for children in a hospital setting. It transports patients to outer space and immerses them in relaxing music as they zap space objects — including "spaceburgers" — that fly toward them. It allows health care providers to adjust the cognitive load according to the patient's needs, meaning they can use a controller to increase the level of distraction during the most stressful parts of a procedure, like right before a needle poke.

COURTESY OF THE BAXTER FAMILY

Blaine Baxter, a patient at Lucile Packard Children's Hospital Stanford, suffered an injury to his arm while racing a go-kart and has benefited from virtual reality to distract him from the pain of dressing changes.

> "As soon as he put the goggles on, sedation was no longer needed."

Research is underway to further quantify the impact VR has on the levels of pain and anxiety that patients experience during vascular access procedures, including blood draws and port access, by comparing the experiences of patients who have used VR with those who have not. "Preliminary results have shown that kids tend to be more cooperative when they are engaged in VR, with less movement, less fear and sometimes even lower pain scores, which can make the experience more positive for the provider and the child," Rodriguez said.

The impact of VR can last beyond the immediacy of a procedure, Caruso added. "Having a less terrifying experience when you go to the hospital can change your behavior for weeks after a procedure," he said. "Things like sleep regression or acting out during the recovery period are associated with distressing perioperative experiences, but by using VR and reducing the fear and anxiety that kids experience before a procedure, we hope to positively impact their behaviors after the procedure."

Now, the CHARIOT team is researching the impact of passive VR experiences, such as watching fish float by, compared with the impact of active games, such as zapping spaceburgers, to understand whether the content itself impacts patients' reported pain and anxiety levels in the clinical setting. Packard Children's is one of the first hospitals to integrate the use of VR as a potential method of anxiety reduction into patients' electronic medical records, which is helping care teams determine which content is most effective for certain populations, according to patient age, procedure and content type.

"Among our patients, there is a subgroup who do well during a procedure with or without VR, a subgroup with minor anxiety where VR helps slightly and they enjoy it, and a subgroup where it makes a profound difference," Rodriguez said. "These patients sometimes come in for a procedure with a 10-out-of-10 level of anxiety and fear, but when we implement VR during a procedure, they report stress levels of 2-, 1- and in some cases 0-out-of-10. Those are the patients we are really targeting with these VR interventions."

What's next

CHARIOT's hospitalwide VR rollout is on track to be fully realized in the new Lucile Packard Children's Hospital Stanford, which is set to open in December, and will continue to expand with additional technologies.

"Our ultimate goal is to take a personalized approach to care by adapting and developing technological interventions for each child's needs," Rodriguez said. New content **See CHARIOT, page 7**

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STANFORD MEDICINE

Immune system changes in pregnancy are precisely timed

By Erin Digitale

Scientists at the School of Medicine have completed the first-ever characterization of the meticulously timed immune system changes in women that occur during pregnancy.

The findings, which were published Sept. 1 in *Science Immunology*, reveal that there is an immune clock of pregnancy and suggest it may help doctors predict preterm birth.

"Pregnancy is a unique immunological state. We found that the timing of immune system changes follows a precise and predictable pattern in normal pregnancy," said the study's senior author, Brice Gaudilliere, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine.

Although physicians have long known that the expectant mother's immune system adjusts to prevent her body from rejecting the fetus, no one had investigated the full scope of these changes, nor asked if their timing was tightly controlled. "Ultimately, we want to be able to ask, 'Does your immune clock of pregnancy run too slow or too fast?'" said Gaudilliere.

The new research comes from the March of Dimes Prematurity Research Center at Stanford University, which aims to understand why preterm births happen and how they could be prevented. Nearly 10 percent of U.S. infants are born prematurely, arriving three or more weeks early, but physicians lack a reliable way to predict premature deliveries.

"It's really exciting that an immunological clock of pregnancy exists," said the study's lead author, Nima Aghaeepour, PhD, instructor in anesthesiology, perioperative and pain medicine. "Now that we have a reference for normal development of the immune system throughout pregnancy, we can use that as a baseline for future studies to understand when someone's immune system is not adapting to pregnancy the way we would expect."

Prior research at Stanford and elsewhere suggested that inflammatory immune responses may help trigger early labor. If scientists identify an immune signature of impending preterm birth, they should be able to design a blood test to detect it.

The study used blood samples collected from 18 women who had full-term pregnancies. Each woman gave four blood samples — one during each of the three trimesters of pregnancy and one six weeks after delivery. Samples from an additional group of 10 women with full-term pregnancies were used to validate the findings.

How each immune cell experiences pregnancy

The researchers used mass cytometry, a technique developed at Stanford, to simultaneously measure up to 50 properties of each immune cell in the blood samples. They counted the types of immune cells, assessed what signaling pathways were most active in each cell, and determined how the cells reacted to being stimulated with compounds that mimic infection with viruses and bacteria.

With an advanced statistical modeling technique, introduced for the first time in this study, the scientists then described in detail how the immune system changes throughout pregnancy.

"This algorithm is telling us how specific immune cell types are experiencing pregnancy," Gaudilliere said.

Brice Gaudilliere

Instead of grouping the women's blood samples by trimester for analysis, their model treated gestational age as a continuous variable, allowing the researchers to account for the exact time during pregnancy at which each sample was taken. The mathematical model also incorporated knowledge from the existing scientific literature of how immune cells behave in nonpregnant individuals to help determine which findings were most likely to be important. The model improved understanding of the immune system much as mapping software that knows which streets are one-way gives better driving directions. "If there are several models that are statistically equivalent, we are interested in the model that is most consistent with our existing knowledge of immunology," said Aghaeepour.

Hopes of finding 'sweet spot'

The study confirmed immune features of pregnancy that were already known. For instance, the scientists saw that natural killer cells and neutrophils have enhanced action during pregnancy. The researchers also uncovered several previously unappreciated features of how the immune system changes, such as the finding that activity of the STAT5 signaling pathway in $CD4^{+}T$ cells progressively increases throughout pregnancy on a precise schedule, ultimately reaching levels much higher than in nonpregnant individuals. The STAT5 pathway is involved in helping another group of immune cells, regulatory T cells, to differentiate. Interestingly, prior research in animals has indicated that regulatory T cells are important for maintaining pregnancy.

The next step will be to conduct similar research using blood samples from women who deliver their babies prematurely to see where their trajectories of immune function differ from normal.

"We're especially interested in understanding more precisely what is happening very early and very late in pregnancy," Gaudilliere said. "We'd like to see if there is really a switch we can catch, a sweet spot where deviation from the norm would be maximal with pathology."

"The immune system does not act in isolation, and we're now very interested in profiling its interplay with other aspects of mothers' biology, such as their genetics, metabolism and the body's microbial communities to come up with a holistic biological clock of pregnancy," Aghaeepour added.

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

Other Stanford authors of the study are basic life science research associate Edward Ganio; postdoctoral scholars David Mcilwain, PhD, and Mohammad Ghameni, PhD; life sciences researcher Amy Tsai; research nurses Martha Tingle and Robin Okada; Dyani Gaudilliere, DMD, clinical assistant professor of surgery; clinical fellow Quentin Baca, MD, PhD; clinical research coordinator Leslie McNeil; David Furman, PhD, adjunct professor at Stanford's Institute for Immunity, Transplantation and Infection; Ronald Wong, PhD, senior research scientist; Virginia Winn, MD, associate professor of obstetrics and gynecology; Maurice Druzin, MD, professor of obstetrics and gynecology; Yasser El-Sayed, MD, professor of obstetrics and gynecology; Cecele Quaintance, administrative director of the March of Dimes Prematurity Research Center at Stanford; Ronald Gibbs, MD, clinical professor of obstetrics and gynecology; Gary Darmstadt, MD, professor of neonatal and developmental pediatrics; Gary Shaw, DrPH, professor of pediatrics; David Stevenson, MD, professor of pediatrics and director of Stanford's March of Dimes center; Robert Tibshirani, PhD, professor of biomedical data science and of statistics; Garry Nolan, PhD, professor of microbiology and immunology; David Lewis, MD, professor of pediatrics; and Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine. Brice Gaudilliere, Winn, El-Sayed, Shaw, Stevenson, Tibshirani, Nolan and Lewis are members of Stanford's Child Health Research Institute. Scientists from Ghent University in Belgium also contributed to this work.

The research was supported by the March of Dimes Prematurity Research Center at Stanford, the Bill and Melinda Gates Foundation, the Ovarian Cancer Research Fund, the Canadian Institute of Health Research, the International Society for Advancement of Cytometry, the National Institutes of Health, the Stanford Child Health Research Institute, the Mary L. Johnson Research Fund, the Christopher Hess Research Fund, and the Food and Drug Administration.

Nolan holds a patent on the mass cytometry technology, which is manufactured by Fluidigm. He also holds equity in Fluidigm.

Stanford's Department of Anesthesiology, Perioperative and Pain Medicine also supported the work. ISM

Nearly all microbes inside us unknown to science, study finds

By Nathan Collins

A survey of DNA fragments circulating in human blood suggests that our bodies contain vastly more diverse microbes than anyone previously understood, according to Stanford researchers.

What's more, the overwhelming majority of those microbes has never been seen before, let alone classified and named, the researchers report.

"We found the gamut," said Stephen Quake, PhD, professor of bioengineering and of applied physics. "We found things that are related to things people have seen before, we found things that are divergent and we found things that are completely novel."

A paper describing the findings was published online Aug. 22 in the *Proceedings of the National Academy of Sciences*. Quake is the paper's senior author. The lead author is graduate student Mark Kowarsky.

Searching for rejection

The survey was inspired by a curious observation Quake's lab made while searching for noninvasive ways to predict whether an organ-transplant patient's immune system would recognize the new organ as foreign and attack it, an event known as rejection. Ordinarily, it takes a tissue biopsy — meaning a large needle jabbed into one's side and at least an afternoon in a hospital bed for observation — to detect rejection.

The lab members figured there was a better way. In theory, they might be able to detect rejection by taking blood samples and looking at the cell-free DNA — bits and pieces of DNA circulating freely in blood plasma — contained therein. Apart from fragments of a patient's DNA, those samples would contain fragments of the organ donor's DNA, as well as a comprehensive view of the collection of bacteria, viruses and other microbes that make up a person's microbiome.

Over the course of several studies, the first of which was published in 2013, Quake and his colleagues collected samples from 156 heart, lung and bone marrow transplant recipients, as well as from 32 pregnant women. (Pregnancy, like immunosuppressant drugs taken by transplant patients, also changes the immune system, albeit in ways both more complicated and less well understood.)

Something weirder

The results of these earlier studies suggested there were identifiable changes to the microbiomes of people with compromised immune systems and that positive tests for the organ donor's DNA were a good sign of rejection.

But there was something else, too — something weirder. Of all the nonhuman DNA fragments the team gathered, 99 percent of them failed to match anything in existing genetic databases the researchers examined.

With that in mind, Kowarsky set about characterizing all of that mystery DNA.

The vast majority of it belonged to a phylum called proteobacteria, which includes pathogens such as *E. coli* and Salmonella. Previously unidentified viruses in the torque teno family, which is generally not associated with disease but often found in immunocompromised patients, made up the largest group of viruses. "We've

NORBERT VON DER GROEBEN

Stephen Quake and his colleagues examined the bits and pieces of DNA in blood plasma and found that 99 percent of the nonhuman DNA fragments didn't match anything in existing genetic databases.

doubled the number of known viruses in that family through this work," said Quake, who also holds the Lee Otterson Professorship in the School of Engineering.

An unsurprising surprise?

Perhaps more important, they identified an entirely new group of torque teno viruses. Among the known torque teno viruses, one group infects humans and another infects animals, but many of the ones the researchers found didn't fit in either group. "We've now found a whole new class of human-infecting ones that are closer to the animal class than to the previously known human ones, so quite See MICROBES, page 8

Students

continued from page 1

the time. Three years ago, she stepped into the position of associate dean of admissions.

"Since then, we have really been working toward furthering these goals," Gibbs said. "That includes creating pipelines and pathways to attract the types of students who best reflect our vision, our goals.

"With the dean's leadership and approval, we've been able to bring in an assistant dean, Judith Ned, to help with this building of a pipeline. We've increased our efforts to reach out to a broader range of individuals."

Ned, EdD, was appointed assistant dean and director of MD admissions in March to supervise operational aspects of medical student admissions and to support and develop new programs to expand outreach and recruitment efforts.

Each year, the MD admissions office receives 7,000 to 8,000 applications. It sends out supplemental questions to each of those and receives back about 6,000 fully completed applications. From that number, 450 to 500 applicants are selected for interviews based on their academic accomplishments, relevant life experiences and personal qualities detailed in their applications.

In 2011, the medical school switched from holding hourlong interviews with faculty members to an interview process known as the multi-mini interview, which involves a series of short interviews over a two-hour period designed to measure character and critical-thinking skills. Since Gibbs took office, an additional, more in-depth interview with a faculty member has been added to this process.

"We think it's really important for students to get a chance to talk to faculty while they are here during the interview process," Gibbs said.

As a final step in the process of choosing applicants to whom admission will be offered, Gibbs said, the reviewers pause to ask themselves the question, "How will this particular student contribute to the learning of others?"

"It is my hope that every single medical student will feel that not only are they learning from those individuals who are teaching up in front of the classroom, but that they are learning from each other," Gibbs said. "And that they bring something unique that enhances the learning environment themselves." **ISM**

PAUL SAKUMA

STEVE FISCH

STEVE FISCH

COURTESY OF BONGEKA ZUMA

STEVE FISCH

STEVE FISCH

(Clockwise from top left) Iris Gibbs said the new class of medical students reflects the school's mission of promoting leadership, innovation, discovery and diversity. Dean Lloyd Minor at the Aug. 25 stethoscope ceremony with first-year medical student Harriet Kiwanuka. Nicholas Hug receives a stethoscope from Lila Hope, president of the Stanford Medicine Alumni Association. New medical students attend the stethoscope ceremony on Alumni Green. First-year medical student Bongeka Zuma was the valedictorian of the inaugural class of Oprah Winfrey's Leadership Academy for Girls in South Africa. In addition to stethoscopes, new medical students received white coats.

Students in new physician assistant master's program begin classes

By Tracie White

A welcome ceremony for the School of Medicine's inaugural class of students in the Master of Science in physician assistant studies was held Aug. 25 on the lawn next to the Medical School Office Building.

Robert Harrington, MD, professor and chair of medicine, and Arturo Molina, MD, Stanford Medicine Alumni Association board member, were among those who welcomed the new class of 27 students. Molina gave the students stethoscopes.

"You are, and forever will be, the first PA master's degree class at Stanford," Harrington said. "You will set the standard for the many classes to follow. We expect you to be great clinicians, teachers, researchers and administrators. You will be leaders in the profession. Don't let that frighten you. Embrace it."

The 30-month program will emphasize training alongside medical students in coursework and clinical care. The students are required to choose an area of scholarly concentration within one of four areas: community health, health services and policy research, clinical research or medical education. The quickly growing field has jumped from 20,000 licensed physician assistants in 1990 to about 115,500 today, according to the American Academy of Physician Assistants. **ISM**

Denise Ros (left) and Marian Padilla are new students in the physician assistant studies program.

KEVIN MEYNELL

Sara Wright (center) and Erin Lencioni (right) attend a ceremony Aug. 25 for new PA students.

Expect the unexpected, Lucy Kalanithi advises students in talk with dean

By Katie Gray

What advice would Stanford physician Lucy Kalanithi, MD, give to students beginning their medical journey?

That was one of the questions Lloyd Minor, MD, dean of the School of Medicine, asked Kalanithi at an Aug. 25 talk for incoming MD and physician-assistant students.

Her answer: to expect the unexpected.

Kalanithi's late husband Paul Kalanithi, MD, a Stanford neurosurgeon, wrote the memoir *When Breath Becomes Air* before dying of lung cancer in March 2015.

"I never thought I'd be speaking so publicly about such personal stuff," she said. She added that while she used to think medicine offered a direct path, she has since learned that many unforeseen events can take people down unanticipated roads. The key to adapting to change is to be open to uncertainty, she said, and to "keep rising to the occasion."

That's exactly what Kalanithi and her late husband had to do four years ago after he was diagnosed with cancer. Since his memoir — in which he reflects on end-of-life care, medical training and meaningful living — was published in January 2016, the book has been on *The New York Times* best-seller list for 66 weeks.

"What struck me most" about the book, said Minor in his opening remarks, "was Paul's perfect articulation of the vivid bond between physician and patient."

"Now I really want to have meaning in my life, and I really want to raise a resilient kid."

Minor, who is collaborating with Kalanithi, a clinical assistant professor of medicine, as part of a winter seminar called "Literature, Medicine and Empathy," also asked Kalanithi what she learned about the patient's perspective during her husband's illness.

"I was desperate for people to empathize and listen," she said. On a given day, while a care provider may be thinking about the long list of cases they need to handle, the patient has waited weeks and weeks for that one encounter, she said.

"There's real data on patient adherence being related to how much they feel allied with you as their provider," she said. "You are the medicine."

Noting

See KALANITHI, page 5

Game challenges players to design on/off switch for CRISPR

By Jennie Dusheck

A team of researchers at the School of Medicine has launched a new challenge for the online computer game Eterna in which players are being asked to design an RNA molecule capable of acting as an on/off switch for the gene-editing tool CRISPR/Cas9.

Molecular biologists will then build and test the actual molecules, based on the most promising designs provided by the players.

Howard Chang

Rhiju Das

A gene editor as powerful as CRISPR could have unexpected effects inside living cells, so it makes sense to turn it off when it's not needed. In addition, an on/off switch might be able to put CRISPR-influenced genes on a sort of timer, activating and deactivating them on a schedule that could mimic the way we schedule taking doses of drugs.

Anyone can play the Eterna RNA-design game. "All you need is a good internet connection, the interest and the time," said Howard Chang, MD, PhD, professor of dermatology and director of the Center for Personal Dynamic Regulomes at Stanford. The center, funded by the National Institutes of Health's Center of Excellence in Genomic Science program, is providing $15 million to support the project.

"Great ideas can come from anywhere, so this is also an experiment in the democratization of science," Chang said. "A lot of people have hidden talents that they don't even know about. This could be their calling. Maybe there's somebody out there who is a security guard and a fantastic RNA biochemist, and they don't even know it."

The challenge to design a CRISPR switch is the latest puzzle offered through Eterna, a game portal that allows players to design virtual RNA structures. Eterna most recently hosted a game event challenging players to build an RNA molecule that could simplify the widespread use of a tuberculosis test.

What is CRISPR/Cas9?

CRISPR/Cas9 is a gene-editing tool derived from bacteria. Researchers in the 1980s discovered that *E. coli*, a species of bacterium that lives in the gut, has a system for reading and damaging viral DNA. When a virus infects a bacterium, it can copy and incorporate segments of the viral DNA into its own genome. (These viral DNA regions are called "clustered regularly interspaced short palindromic regions," or CRISPR.) Just as our own immune systems can use antibodies to remember previous infections, the viral DNA in CRISPR regions helps *E. coli* bacteria recognize a subsequent viral infection. When a bacterium's RNA molecules recognize the viral DNA, they guide the CRISPR/Cas9 complex to that DNA, and the bacterium's Cas enzymes destroy the viral DNA by cutting it.

In 2012, researchers found a way to deploy the bacterial CRISPR/Cas9 immune system — including CRISPR, a protein called Cas9 and a "guide" RNA — to recognize, cut and replace any DNA sequence. Since then, the CRISPR/Cas9 system has enabled rapid gene editing projects in everything from viruses to corn to human stem cells.

How a CRISPR on/off switch might be used

"CRISPR is a technology for cutting or binding DNA," said Chang. "But you don't want it to be on all the time." It would be useful to have a switch that could turn gene activity on and off on some sort of schedule. A doctor often tells a patient to take a drug twice a day for two weeks. But if the "drug" were generated by the patient's own genes, he said, small molecules might be used to switch on that gene activity for an hour or two twice a day for two weeks and then stop.

Right now, Chang said, if someone used CRISPR/Cas9 to engineer cells to activate a gene, it would be hard to know how much the gene is being turned on. Plus, he said, the gene would be on all the time. "We just hope everything works out and it's the right amount. But that's a little scary, right?" said Chang.

CRISPR's not just about breaking the gene to turn it off, said William Greenleaf, PhD, associate professor of genetics. "A switch on the CRISPR/Cas9 system can control how the genes are being expressed — that is, when and where."

Where the RNA molecule comes in

In the new Eterna challenge, called OpenCRISPR, players will design a guide RNA molecule that leads CRISPR to the right sequence of DNA for editing or binding. "The RNA is the part that confers gene specificity. It's the thing that says, 'Go after gene A, not gene B,'" said Chang.

The difficulty for Eterna players is to come up with an RNA molecule that does several things, said Greenleaf. The guide RNA has to be recognized by the CRISPR-associated enzyme. The CRISPR-enzyme system has to be able to recruit biochemical activity to the targeted gene. And lastly, the activity of the CRISPR-enzyme system has to be controlled by a small-molecule drug, so there needs to be a "binding pocket" for that small molecule. The RNA molecule has to function so that the CRISPR system is active when the small-molecule drug is present and inactive when it's not. So far, experts have not been able to create such a drug-activated CRISPR, which is why Chang and Greenleaf are calling on the community of Eterna gamers for help.

The new puzzle will be quite different from the recent challenge in which Eterna players had to design a molecule that could do a mathematical calculation for a tuberculosis diagnostic test. "The CRISPR puzzle actually should be pretty easy to solve in silico, even for new players who get to the switch design levels," said Rhiju Das, PhD, associate professor of biochemistry and principal investigator for Eterna.

"The Eterna game is a powerful way to engage lots and lots of people."

From in silico to in vitro: an iterative process

How those Eterna-designed switches will behave in living cells is a big question. Das said the team will be asking players for different possible solutions to the same problem. "We're not sure yet if there will be unforeseen problems with the Cas9 protein experimentally. That's partially why we want as many diverse solutions as possible for the Greenleaf and Chang labs to test, even in this pilot round," Das said.

It will be an iterative process, said Greenleaf. His Stanford lab will test the first round of solutions and then return these data to the players with refinements that will guide their design work.

"We're hoping for 10,000 to 100,000 players to contribute 10 solutions each. If we get that many, we'll indeed work to get that many synthesized and tested," Das said.

Out of the ivory tower

One of the goals of Stanford's Center for Personal Dynamic Regulomes is to get people interested in science, said Chang. "The Eterna game is a powerful way to engage lots and lots of people," he said. "They're not just passive users of information but actually involved in the process."

Like other computer games, Eterna allows players to accumulate points, build expertise and advance to higher levels. The best players have a chance of having their designs implemented in the lab.

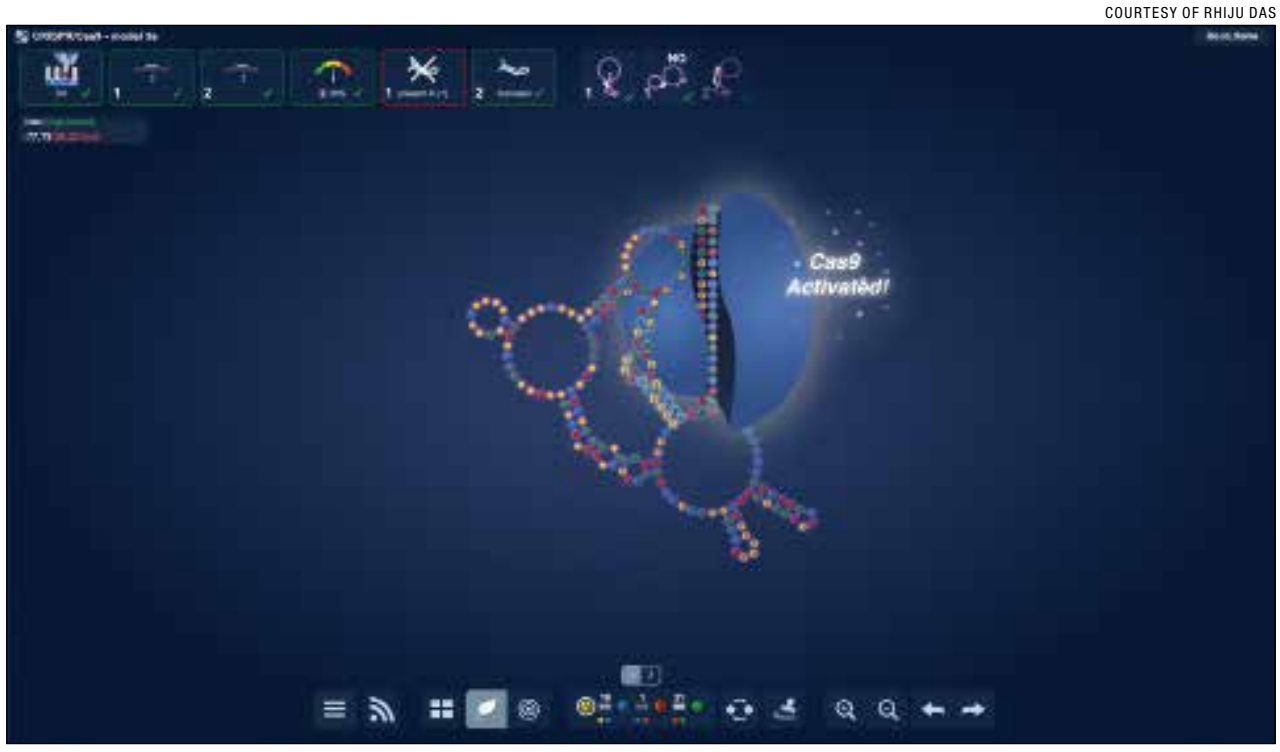
One thing that makes the project exciting, said Chang, is that it is an experiment in the sociology of science. "There is a misconception of science as something that happens in an ivory tower by someone in a white coat with a long beard. And they are saying things and drawing things that nobody understands. But it's not like that! It's really like a puzzle that anybody can get engaged with," he said.

Anyone interested in playing Eterna can sign up at http://www.eternagame.org.

In addition to the funding from NIGMS and Stanford's Center for Personal Dynamic Regulomes, the new Eterna challenge is being launched with collaborative support from the Innovative Genomics Institute at the University of California-Berkeley.

Stanford's departments of Biochemistry and of Genetics also supported the work. **ISM**

COURTESY OF RHIJU DAS



A new challenge on the Eterna computer game allows players to try to design a molecule that can turn CRISPR gene-editing on and off.

Kalanithi

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that the memoir describes this responsibility as both an enormous blessing and a burden, Minor asked Kalanithi about physician wellness. She said medical institutions have a clear role to play in removing the stigma of asking for help.

STANFORD VIDEO

Lucy Kalanithi, whose late husband wrote the best-selling memoir *When Breath Becomes Air*, talks with Lloyd Minor on Aug. 25.

"If you feel burned out, or if you feel depressed or anxious, it's not that there's something wrong with you. It's a greater system issue," she said, adding that Stanford Medicine is becoming a national leader in the field of physician wellness.

As for her own well-being, Kalanithi talked about navigating life in the years since the death of her husband. She said she thinks often about how to describe him to their daughter, Cady, who is now 3.

"I'm really happy that he wrote this book because he did it in part for her," she said.

In response to an audience member's question about whether her definition of happiness has changed since losing Paul, she said, "I used to think, 'I want to be happy all the time' or 'I want to raise a happy kid,'" she said. "Now I really want to have meaning in my life, and I really want to raise a resilient kid." **ISM**

Fear

continued from page 1

time seems to slow down.

But there's more to fear than a constellation of peripheral bodily signals, Huberman said. It's a state of mind, as well, a holding pattern designed to maintain heightened arousal while you figure out what to do next. To neuroscientists, that means it's also a state of the brain, shaped by eons of evolutionary trial and error during which the punishment for failure to respond appropriately and quickly was often death, not to mention fewer viable offspring.

Huberman wants to learn more about fear by identifying the neural circuitry underlying it, and pinpointing the circuits' settings during episodes of fear. In the long run, Huberman also hopes to help people gain more control over irrational fear, a response that can get tripped off so often or so severely it hampers healthy coping.

To study fear, one must induce it, which Huberman is doing. Having spent the last 20 years or so studying the neurobiology of vision, he's taking a mainly visual approach, with the help of a virtual-reality chamber his team created from scratch.

Vision is our dominant mode of sensation, Huberman noted.

"Nearly 40 percent of the human brain is dedicated to processing visual information," he said. So it stands to reason that visual information about a real or imagined threat gets VIP treatment in the brain.

But very little has been done in charting the flow of information from visual input through the deeper centers in the brain where fear is generated, processed, acted on and overcome, Huberman said. "There's still so much we just don't know."

We do know that images landing on the retina trigger signals in nerve-cell relays that, after numerous processing steps, yield a conscious perception of what we see. But we've also evolved specialized, faster forms of response to visual threats. Faced with a poisonous snake or a hungry beast, you don't want to wait until you've been devoured or injected with a lethal toxin before you get around to stepping back, starting to run or putting up your dukes. You need to register right away that something bad is happening, and figure out exactly what it was later.

There's an alternate fast-track route, from the retina to a well-studied brain structure, the amygdala, which speedily carries out many functions, including flagging threats. Signals from the amygdala can trigger secretion of stress hormones from the adrenal glands into the bloodstream, unlocking loads of energy-rich glucose stored in the liver for rapid uptake by the muscles.

The mice that roared

Other important, though not as well-studied, brain centers are involved in visual threat detection and response. Lindsey Salay, a graduate student in Huberman's laboratory, has identified one of those centers, right smack in the middle of the brain. Ironically, the brain center Salay found responds to fear-inducing stimuli by stiffening the spine.

One thing mice are afraid of — innately so, no previous training required — is aerial predators: hawks, owls and so forth. Put a mouse in an open field, and it's a sitting duck. Within a second of perceiving an airborne predator, that mouse almost invariably makes a decision to either freeze, which it hopes will make it harder to detect, or make an immediate run for shelter if it's available. There aren't a whole lot of other promising options.

To determine how brain activity changes in the presence of a visual threat, Salay employed a laboratory mock-up of a predator's approach: a mouse-scale arena akin to an open field, with a video screen covering most of its ceiling. On that screen could be shown an expanding overhead disk that simulates an approaching bird of prey.

A postdoctoral scholar in Huberman's lab, Melis Yilmaz Balban, PhD, created this contraption while a student at Harvard and then CalTech. In a study published in 2013, Yilmaz Balban showed that mice sighting a dark overhead expanding disk either run for cover or freeze for an extended period.

Salay compared the brain activity of mice that had been exposed to this "looming predator" for a few minutes with that of mice that hadn't. She located a particular region called the ventral midline thalamus, or vMT, that became activated in the presence of the overhead expanding disk but was relatively quiescent in its absence.

Salay found that despite its activation by fear-inducing stimuli, the vMT, to which humans have an analogous structure, wasn't just another cog in the brain's run-and-hide machinery. To the contrary: If you stimulate mice's vMT sufficiently, she observed, instead of freezing or running for cover, they become uncharacteristically inclined to stand their ground. They remain right out there in the open and start rattling their tails.

"You can actually hear their tails thumping on the floor or against the wall of their enclosure," said Salay. This defiant behavior, displayed by macho male mice just before they start fighting or by nursing mouse moms when a strange male intrudes into their space, is observed only rarely in regular mice under simulated aerial attack, and then only after they've ducked into a shelter they can crouch in, safe and sound.

The vMT-stimulated mice also run around more out in the open. That, as well as the tail-rattling, would make the mouse much more visible and tantalizing to a real attacker in real life.

Call it "courage."

Said Salay, "It's like flipping a switch from cowardice to bravado. The vMT is the switch."

And the mice *like* playing Mighty Mouse. Given a choice between two locations, one where they get their vMT stimulated and another where they don't, they preferentially head for the one that generates stimulation.

TOMER HANUKA

Stanford researchers are planning to study fear by inducing it under controlled conditions with the help of virtual reality technology.

Humans apparently like it, too. According to studies from the early 1960s, patients preferred stimulation of a brain region analogous to a mouse's vMT over stimulation of any other brain area tested, including ones associated with sexual arousal. Oddly, when asked to describe the sensation they perceived when it was stimulated, they didn't recount titillating tales associated with pleasure. Instead, they reported feeling "frustration and mild anger." Hmmm. And they *liked* it. This could explain a lot about our attraction to sports, not to mention the chemistry in a person's previous relationships.

In short, the vMT is like Popeye's spinach. Activating it appears to bring on a bird-flipping rush of righteous defiance.

The lion and the gazelle

A gazelle running for its life and the lion chasing it are, in many respects, in similar physical states. Both animals' adrenal glands are pumping furiously, and both animals' livers are shoveling tons of glucose into their bloodstreams. Their hearts are pounding, their breathing is accelerated, their senses are heightened.

So, what's the difference? Well, for one thing, their state of mind. The lion wants to be there; the gazelle really doesn't.

> "Our goal isn't just to learn about fear, but to test ways of engaging in more adaptive coping."

Activating the vMT appears to turn a mouse's mental state in the face of a harrowing situation from gazelle-like to lionlike. What if you could do that in humans, too?

"We're hoping to learn how to turn gazelles into lions," Huberman said. Doing that doesn't necessarily require gaining direct physical access to a person's vMT. That's lucky, because you can't just tuck a bunch of electrodes into the middle of people's heads and crank up the juice. So instead, Huberman and his teammates are planning to induce fear under controlled conditions; monitor some of the more easily accessed autonomic states that accompany it; and see if there are reliable, testable ways of reducing it. For this, they've turned to virtual reality.

VR is uniquely capable of capturing visual experiences so that the full sphere of visual input gets reproduced: Put on the goggles, hit the "play" button, and wherever you look, you'll see a 3-D replication of pretty much whatever you would have witnessed in the real-life scenario. Audio input, easily provided, further enhances the experience.

Huberman's group equipped its VR chamber with an observation window so investigators can monitor participants in real time, and with padded walls in case a participant reflexively makes a run for it under the mistaken impression that an open field lies ahead.

After filling out questionnaires concerning their current and general levels of anxiety and fear, participants will be fitted with sensors and filmed as they undergo a series of unsettling VR scenarios, of which the shark encounter is just one. Afterward, they'll be coached in one of a variety of ways that might help them dial down the typically uncomfortable, often decision-hindering, and sometimes debilitating autonomic reactions that, given the corresponding mental state, we categorize as fear. Then they'll be tossed back into the VR chamber for a repeat round of the hair-raising episodes to see if the training worked.

Huberman and his colleagues hope to run hundreds of healthy, normal participants through this just-completed VR chamber in the next year. The idea is to establish baselines for the various parameters being measured.

Eventually Huberman hopes to introduce hundreds or even thousands of participants, including people with post-traumatic stress disorder, generalized anxiety disorders or a variety of phobias, to the chamber.

Many people carry around uncomfortable levels of fearfulness with them even when they're not contending with an oncoming 30-foot-long shark. During their lifetimes, about 5 percent of all Americans will be diagnosed with a severe anxiety disorder, nearly 8 percent will receive a diagnosis of PTSD and more than 10 percent will suffer from a phobia. They can't simply calm themselves by repeating, "It's not real" or "This isn't really a threat."

Invoking journalistic privilege, I volunteered to be the first person to test the waters, as it were, by being treated to a walk-through of the entire sequence of scare scenarios. So there I stood in the customized chamber, begoggled, headphoned and festooned with multiple electrical leads monitoring my heart rate, breathing and sweat output.

Cameras in the room's upper corners spied on my face and hands, while the goggles fed me virtual-reality footage. (They were also checking my pupil size, a good indicator of a person's arousal level: the wider the pupil opens, the higher the arousal.) Watching through the observation window was Yilmaz Balban, the creator of the "looming predator" paradigm.

"When I put mice in a box and showed them a defined stimulus — an overhead expanding disk — they exhibited an easily identified and measurable behavioral response: freezing or running for cover," she said. "Now, I wanted to put humans in a box and see what happened and whether that could be measured, too."

So she conducted an online survey asking people what they're afraid of, and received lots of feedback: Plenty of us are afraid of heights, spiders, snakes and vicious dogs. Oh, and sharks.

Scare scenarios and high hopes

In October 2016, Huberman and a few members of his team traveled to Guadalupe, an island off the coast of Baja California where great white sharks abound at that time of year. Accompanying them was famed Hollywood photographer and skilled open-water shark diver Michael Muller. Huberman, Muller and other divers entered a cage that was then submerged 30 meters straight down into a school of great whites. From that submersible enclosure, Huberman shot 360-degree "spherical video" (wherever you look, you see whatever was there when the camera was filming the scene). Muller and a few other divers left the cage to get very up-close video of the 14- to 20-foot long, 2-ton creatures.

"Visually speaking, it's about as real as being there," Huberman said. "The only difference is you don't get wet — although some people sweat a lot." I watched this episode unfold all around me during my VR experience.

I was also subjected to scenarios in which I was perched on a branch of a very tall tree hundreds of feet above the sidewalk, or seated next to a vicious, toothy pit bull that "attacked" my arm. Rounding out the picture were computer-generated but nonetheless ultra-realistic bouts of leaping off a plank several stories above the ground, and fending off attacks by a large hairy spider with the rough

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Fathers

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The study was published online Aug. 30 in *Human Reproduction*. Michael Eisenberg, MD, an assistant professor of urology, is the senior author. The lead author is Yash Khandwala, a medical student at the University of California-San Diego who was a research scholar in Eisenberg's lab at Stanford when the analysis was done.

The National Vital Statistics System records births and deaths reported by all 50 states, as well as self-reported maternal and, where available, paternal ages, levels of education and race and ethnicity of the parents. While the CDC periodically produces reports on maternal statistics, little information about newborns' dads has been available.

Older dads and college degrees

Between 1972 and 2015, the researchers found, the average paternal age at the time of an American child's birth grew from 27.4 years to 30.9 years. Asian-American dads — and in particular, Japanese- and Vietnamese-American dads — are the oldest, at 36 years of age on average. Paternal age rose with more years of education; the typical newborn's father with a college degree is 33.3 years old.

Over the same time period, the share of newborns' fathers who were older than 40 doubled from 4.1 percent to 8.9 percent, while the share who were over 50 rose from 0.5 percent to 0.9 percent.

Similar trends of increasing age have been reported in other industrialized countries.

The steadily advancing age of newborns' fathers is likely to carry public-health implications as well, Eisenberg said. A rising paternal age can affect the total number of children a man will have, which can impact the demographics of the population. In addition, he said, "every potential dad acquires an average of two new mutations in his sperm each year. And there are associations between older fatherhood and higher rates of autism, schizophrenia, chromosomal abnormalities, some pediatric cancers and certain rare genetic conditions."

On the flip side, he noted, older fathers are more likely to have better jobs and more resources, more likely to have reasonably stable lifestyles and more likely to live with their children and, thus, be more involved in child-rearing.

Ages of new moms increasing, too

"Maternal ages at birth have been increasing, too," Eisenberg said. "In fact, they've advanced even more than paternal ages have in the same time frame. This may be a consequence of women waiting longer to get married or putting off childbearing as the years they spend in higher education increase and as careers become more central to their lives. The result is that the average age difference between moms and dads has been shrinking, from 2.7 years in 1972 to 2.3 years in 2015."

This convergent pattern appears to apply to all racial, regional, age and education categories, he said. "We've seen a lot of changes in the last several decades. Contraception is more reliable and widespread. Women have become more integrated into the workforce. This seems to be reflected in an increasing parity in parental ages over the last four decades."

Advancing parental age leaves fewer years for childbearing and is likely to exert a follow-on effect of reducing the average family size over the long haul, with potentially huge economic and public-health ramifications, Eisenberg said.

"Fewer people being born means fewer productive workers a generation down the road," he said. "This can obviously have profound tax and economic implications."

While parental-data reporting to the National Vital Statistics System by some states was spotty in the early years of the period under study, it's been running at virtually 100 percent since 1985, at least for mothers, said Eisenberg. In 2015, the latest year available, information about newborns' fathers was missing in one of every nine births. That could be because the father was unknown or because the mother didn't wish to report his name or any details about him, Eisenberg said.

SOLOVIOVA LIUDMYLA / SHUTTERSTOCK.COM

Men over the age of 40 now account for about 9 percent of all U.S. births, according to a new study.

It matters. Evidence indicates that, on the whole, young children whose paternal data appears in their birth records have better health outcomes.

Paternal-data reporting rates vary according to mothers' race, ethnicity, age, education and regional location, the analysis showed, with the reporting rate for African-American newborns consistently the lowest for all races. Over the past decade, African-American mothers under the age of 20 reported paternal data only half the time. However, the rate of paternal reporting for children born to African-American mothers has grown from its low of 63 percent in 1985 to a current rate of 70.9 percent, Eisenberg said.

Overall paternal reporting for U.S. births has risen to its current 88.4 percent since reaching a nadir of 85.5 percent in 1991.

The youngest dad recorded during the 44-year period covered in the study was 11 years old; the oldest was 88. But the world-record holder, Eisenberg said, is a gentleman from India who in the last decade fathered two children at the age of 94 and 96 with a wife who was in her late 50s. "Unfortunately, they wound up separating," he said.

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

Other Stanford co-authors of the study are biostatician Chiyuan "Amy" Zhang, MPH, and Ying Lu, PhD, professor of biomedical data science.

Stanford's Department of Urology supported the work. **ISM**

Fear

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equivalent of a baseball bat.

In the latter scenario, you're supposed to play a complicated game in which you aim a wand at a wall to make lit-up squares flip to dark and vice versa. But that's just a distraction. You soon become aware that there's a gross, hairy tarantula on the wall behind you. At least they give you a bat to smash it with. I chose to do so. But it was rigged. I discovered the bat couldn't kill or even dent the damned spider. It just caused the spider to leap off the wall and fly into my face or onto my clothes. You could say I was moving around a lot during this episode.

Afterward, Yilmaz Balban told me that I was most pumped, autonomically speaking, while I was locked in gladiatorial combat with the spider.

"I wasn't scared, though," I blurted out, not without pride and, perhaps, a hint of emotional amnesia.

"You were aroused."

I guess that's how it feels to have your vMT stimulated.

After spending over an hour under the spell of a pair of VR goggles, ripping them off is somewhat of a shock — a rapid splashdown into what shrugging techies, videogame addicts and others for whom ordinary reality has been demoted call "the default world."

To ease my re-entry, Huberman walked me down the hall into his office, offered me a seat in a body-contoured plastic chair and slapped some headphones on me. For the next 15 minutes, I was guided through a recorded, customized audio de-stressing session consisting largely of controlled-breathing and relaxation exercises. It worked so well that for the last several minutes I didn't know where I was, or care.

It was a preview of what is to come. Huberman wants to put science to work developing tools for systematically reducing pathologic fear and anxiety. After their exposure to the battery of threats, participants will receive training in various methods for doing that.

"Our goal isn't just to learn about fear, but to test ways of engaging in more adaptive coping — to help people make more logical decisions in the face of fear," Huberman said. "There are a lot of practices already out there that claim to reduce anxiety. We know they have some utility." But rigorous testing of these methods isn't easy, he said, due to the lack of standardization and difficulty in measuring their component inputs or their outcomes with any exactitude.

One of several potential fear-countering techniques the researchers will test is controlled breathing. Choppy, rapid breathing stimulates arousal, whereas deep, slow breathing patterns with emphasized exhalation purportedly induce calm.

"We're not talking about meditation," Huberman said. "This is about how you can control your state by action, not inaction — how to cope when you have to make a split-second decision or when you are stressed and know it but can't seem to snap out of it. We want to come up with protocols that prescribe exact, testable steps: for instance, inhale for two seconds, hold for two seconds, exhale for four seconds, and don't worry about keeping a mantra in mind — how would we measure that, anyway? Behaviors like breathing, I can measure carefully."

Huberman sees a tremendous potential for testable fear-reduction techniques. "We're talking about testing and developing practices that are teachable, portable and free," he said.

But, he adds, "We're not trying to 'cure' fear. We want to develop coping tools for reducing irrational fear.

"Fear can keep you alive. Most people should stay away from sharks." **ISM**

A version of this article appears in the summer 2017 issue of Stanford Medicine *magazine.*

Chariot

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and more VR headsets will be available in the new hospital, including additional headsets specifically for patients with chronic conditions who are using VR as a relaxation technique to escape the hospital environment. For patients who are interested in watching their IV placements and minor procedures as they happen, CHARIOT has recently introduced augmented reality headsets — a technology that layers visual enhancements atop existing reality. Their first AR experience shows two avatars demonstrating the process of peripheral IV placement. The goal is to expand the availability of AR programming in the new hospital. A new volunteer program intended to support child life specialists with patient distraction and VR headset setup is being implemented within perioperative services and will expand in the new building to support the broader deployment of distraction-based technologies.

In addition, Rodriguez and Caruso are in discussions with local technology companies about how to share these technologies beyond Packard Children's. "Our overarching mission is to help as many children as we can and make our discoveries available to other people and other hospitals," Caruso said. "Having the hardware and software tools at the ready would make this a reality."

Rodriguez hopes that the program will continue to improve patients' experiences as it evolves. "If you can take someone and alleviate their fear, it makes everything we're doing worthwhile," he said.

Juno VR LLC worked with CHARIOT to develop Spaceburgers. GameHearts LLC worked with CHARIOT to develop Sevo the Dragon. MineyMoe worked with CHARIOT to develop the augmented reality IV insertion instructional experience. Headsets, smartphones and funding have been provided by Starlight Children's Foundation, thanks to support from Star Wars: Force for Change, Google and Niagara Cares. Additional funding came from the Auxiliaries Endowment at Lucile Packard Children's Hospital Stanford, Bank of America and The Traverse Foundation. **ISM**

New Center for Health Education could benefit learners worldwide

By Ruthann Richter

Stanford University launched a new Center for Health Education on Sept. 1, providing online teaching tools for a variety of learners worldwide — from highly credentialed professionals seeking advanced curricula to community health workers in areas with no access to conventional educational resources.

A collaboration between the School of Medicine and the Office of the Vice Provost for Teaching and Learning, the center is directed by Charles Prober, MD, the medical school's former senior associate dean for medical education and a pioneer in advancing health education through digital training.

"Thanks to Charles' visionary leadership, Stanford Medicine has earned an international reputation for collaboratively building innovative curricula and blended learning experiences," said Lloyd Minor, MD, dean of the School of Medicine. "The new Center for Health Education will capitalize on this progress through a strong partnership with the vice provost's office, helping extend advances in understanding achieved by our world-class faculty to learners far beyond our campus boundaries."

The center will use the resources and expertise developed by the vice provost's office over the past five years, including experts in instructional design, program development and learner support. The vice provost's office will be the center's home base. Prober will serve as both the founding director of the center and the senior associate vice provost for health education within the office.

"We are very pleased to serve the School of Medicine and the field of medicine in this way," said John Mitchell, PhD, vice provost for teaching and learning. "An important part of our mission is to make Stanford's expertise more broadly available. This new center provides an opportunity to do that through meaningful impact on human health."

Charles Prober

John Mitchell

The center's offerings ultimately may range from free content in resource-poor countries to fee-based certificate and degree programs in developed economies, Mitchell said, and will be funded by private foundations and philanthropy, tuition and, in some cases, research sponsorships.

Building on existing programs

Prober noted that the proliferation of smart devices into the farthest reaches of the globe has made it possible to distribute health information broadly, with content tailored to address a wide variety of audiences. A topic like nutrition education, for example, can be tailored to reach medical students, patients, health professionals in continuing medical education or individual citizens in rural communities in some of the world's most impoverished countries.

"Anything we create of inherent value for health care should be repurposed for health care for all, including developing countries," he said.

The center will build upon existing programs developed by the medical school and the vice provost's office and also expand partnerships with other organizations, including academic institutions, governmental agencies and nonprofits both in the United States and abroad.

The center will expand Stanford's Digital Medical Education International Collaborative program, which aims to improve health education by creating high-quality, accessible content for use in developing countries. Digital MEdIC already has a strong presence in India, where Sakti Srivastava, MD, associate professor of surgery and director of the program, has been building partnerships with public and private medical schools, nonprofits and government agencies to make online and simulation-based resources about health more widely available.

Similarly, Maya Adam, MD, a lecturer in pediatrics, is now expanding the Digital MEdIC program in South Africa by disseminating digital teaching tools on nutrition, pregnancy, breastfeeding and HIV management that can be used by community health workers and local women who might not otherwise have access to this information.

Online and interactive

The new center also will promote courses that combine online and interactive learning. For example, students at Stanford's medical school now learn biochemistry by watching short videos on their own time and then attending interactive class sessions to discuss the material. Whereas attendance in biochemistry lectures once hovered between 20 and 30 percent (not unusual at medical schools), some 95 percent of students now attend the interactive sessions. The School of Medicine has been collaborating with other medical schools in developing a similar approach to teaching microbiology and other topics in basic science.

While the center will initially draw content from the School of Medicine, it eventually will include other Stanford faculty whose work touches on health and wellness — for example, experts on climate change, economics, psychology and international law.

"We invite faculty from other Stanford schools with an interest in health to join in the effort and help us make the most effective contribution possible to world health," Mitchell said. ISM

OF NOTE

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

MICHELE BARRY, MD, professor of medicine, senior associate dean of global health and director of the Center for Innovation in Global Health, will receive the Elizabeth Blackwell Medal from the American Medical Women's Association in March. The association's highest award, it recognizes a female physician who has made outstanding contributions to support women in medicine. In addition, Barry was appointed to a three-year term on the National Academies of Science, Engineering and Medicine Board on Global Health. Barry was also elected to a two-year term, starting in 2020, as chair of the Consortium of Universities in Global Health, a coalition of 145 academic institutions and other organizations that address global health challenges.

VICTORIA BOGGIANO, a medical student, was named a 2017 Pisacano Scholar by the Pisacano Leadership Foundation. The award, which includes up to $28,000 in scholarship funds, is given to medical students committed to family medicine who demonstrate leadership, academic excellence, strong communication skills, integrity and a commitment to community service.

Michele Barry

Victoria Boggiano

MICHAEL KAPILOFF, MD, PhD, was appointed associate professor of ophthalmology, effective July 10. His research examines the molecular and cellular responses of retinal ganglion cells and cardiac myocytes to disease. His translational efforts include the development of gene therapies for the treatment of retinal diseases and heart failure.

ARNOLD MILSTEIN, MD, professor of medicine, was appointed to the California Future Health Workforce Commission. The commission, comprised of leaders in health, education and workforce development, will develop a strategy to strengthen the health workforce with a focus on primary care, behavioral health and aging. He directs Stanford's Clinical Excellence Research Center.

ANISHA PATEL, MD, was appointed associate professor of pediatrics, effective July 1. Her clinical focus is in general pediatrics. Her research interests include developing and evaluating interventions and policies to prevent childhood obesity.

ERQI POLLOM, MD, was appointed assistant professor of radiation oncology, effective July 1. Her research and clinical interests include stereotactic body radiation, breast cancer, brain tumors and radiosurgery.

VIVIANNE TAWFIK, MD, PhD, was appointed assistant professor of anesthesiology, perioperative and pain medicine, effective July 1. Her clinical interests include the treatment of chronic pain, complex regional pain syndrome and peripheral nerve injury, and her research focuses on the interaction between the immune system and the nervous system following injury. She is the assistant director of the anesthesia residency research track. ISM

Michael Kapiloff

Arnold Milstein

Anisha Patel

Erqi Pollom

Vivianne Tawfik

Microbes

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divergent on the evolutionary scale," he said.

"I'd say it's not that baffling in some respects because the lens that people examined the microbial universe with was one that was very biased," Quake said, in the sense that narrow studies often miss the bigger picture. For one thing, researchers tend to go deep in the microbiome in only one part of the body, such as the gut or skin, at a time. Blood samples, in contrast, "go deeply everywhere at the same time."

For another, researchers often focus their attention on just a few interesting microbes, "and people just don't look at what the remaining things are," Kowarsky said. "There probably are some interesting, novel things there, but it's not relevant to the experiment people want to do at that time."

It was looking at blood samples in an unbiased way, Quake said, that led to the new results and a new appreciation of just how diverse the human microbiome is.

Going forward, Quake said, the lab hopes to study the microbiomes of other organisms to see what's there. "There's all kinds of viruses that jump from other species into humans, a sort of spillover effect, and one of the dreams here is to discover new viruses that might ultimately become human pandemics." Understanding what those viruses are could help doctors manage and track outbreaks, he said.

"What this does is it arms infectious disease doctors with a whole set of new bugs to track and see if they're associated with disease," Quake said. "That's going to be a whole other chapter of work for people to do."

Quake is a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Stanford Cancer Institute and the Stanford Neurosciences Institute, as well as a faculty fellow of Stanford ChEM-H.

Other Stanford co-authors are Yasser El-Sayed, MD, professor of obstetrics and gynecology; Yair Blumenfeld, MD, associate professor of obstetrics and gynecology; David Stevenson, MD, professor of pediatrics; Gary Shaw, DrPH, professor of pediatrics; postdoctoral scholar Joan Camunas-Soler, PhD; graduate students Michael Kertesz, Winston Koh, Wenying Pan and Lance Martin; senior research scientists Norma Neff, PhD, and Ronald Wong; and research assistant Jennifer Okamoto. ISM