INSIDE STANFORD MEDICINE

Volume 9, No. 17 ■ September 25, 2017 ■ Published by the Office of Communication & Public Affairs

A yearlong program pairs first-generation medical and graduate students with mentors.

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Adaptive optics brings eye disease into focus

By Krista Conger

"What are you going to do for my son?" the woman asked.

It was 2007 and the researcher in the hot seat was physicist Alfredo Dubra, PhD, then a research associate at the University of Rochester in New York. Dubra was pioneering new ways to peer into the human eye to identify damage to the light-sensing cells that make up the retina.

As part of his research, he'd just examined the woman, who was suffering from an inherited retinal disease. She had already lost most of her sight, and Dubra knew that a similar fate likely awaited her teenage son.

"In that one moment, that single question fundamentally changed the way I do research," Dubra recalled. "That moment is imprinted upon my memory."

In the years since, Dubra, now an associate professor of ophthalmology at Stanford, has become a leader in the field of adaptive optics — an imaging technique that uses Cold War-driven advances in astronomical telescopes to view a whole new galaxy of cells and anatomical structures in the human eye. Normally, these cells, closeted at the back of the eye, are surprisingly hard to see in any fine detail. But adaptive optics transforms blurry, gray images reminiscent of static on a poorly tuned television into a clearly defined landscape in which an individual cell's structure, location and even functional status can be determined. It's likely to change lives by permitting researchers and clinicians to diagnose, monitor and treat devastating, degenerative retinal and neuronal diseases earlier and more effectively.

"The advances that Alf and his team have made in adaptive optics have changed the way we in the field look at photoreceptors in the retina," said Michel Michaelides, MD, professor of ophthalmology at University College London and one of the leaders of the college's gene therapy trial pipeline for inherited retinal diseases. "There really is no parallel for the quality of images we can now see."

More than 10 million Americans are affected by as-yet-incurable vision loss, and Dubra is quick to connect the dots between these people and his lab's (and life's) work.

"I will never forget that woman and her son," Dubra said. "All too often patients are just abstract concepts to physicists and engineers like me, and it's easy to stay immersed in the technology and forget the end goal. That's why it's vitally important to have regular contact with people who are visually impaired, and who desperately need help. These people are going blind."

Through a child's eyes

Not long ago, Dubra, who was born and raised in Uruguay, was one of those people. As an infant, he suffered from a severe case of strabismus, or crossed eyes. He needed several surgeries before age 3 to correct the misalignment and ensure that the visual cortex of his brain learned to properly interpret the signals around him. Untreated, strabismus can lead to blindness if the developing brain abandons attempts to decipher images from the affected eye or eyes.

"When I was about 7, I was leaving a visit to the eye doctor to see how my eyes were developing, and I burst into tears," Dubra said. "My father tried to find out what was wrong,

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BRIAN SMALE

Alfredo Dubra is a leader in the field of adaptive optics, an imaging technique that uses Cold War-driven advances in astronomical telescopes to view cells and anatomical structures in the human eye.

In mom's pouch, baby marsupials 'drink' placenta to enhance their development, researchers find

By Krista Conger

Modern mothers, whether they be human or mouse, might be forgiven for envying marsupial mamas. Rather than enduring a long pregnancy and the birth of a relatively well-developed — and comparatively large — baby, kangaroos, wallabies and their ilk blithely pop out offspring after pregnancies measured in days rather than months.

These tiny, almost formless creatures then make their own intrepid way up to the mother's pouch to nestle politely and nurse for sometimes as long as a year.

MB RENFREE

Scientists studying the tammar wallaby discovered that the females express genes important for fetal development in their milk.

For decades, researchers assumed that this premature eviction from the womb left little or no role for the placenta, which in most mammals tightly links the physiological processes of the mother and the fetus to support the fetus's many stages of development. These mammals are called eutherian mammals to distinguish them from the evolutionarily distant marsupials. In the past decade or so, however, it has become apparent that marsupials do sport their own, rudimentary version of this important organ.

Now researchers at the School of Medicine and the University of Melbourne in Australia have collaborated to learn that marsupials have evolved a clever trick to support their need for a shortened pregnancy and a long lactation period. In short, female marsupials express genes important for fetal development that are normally found in the later stages of the eutherian placenta in their mammary glands instead — a kind of handoff of the developmental baton from womb to milk that suits their unique, savanna-hopping lifestyle.

"This research basically shows that the placenta, while really different-looking in the marsupial, has many of the functions of the eutherian," said Julie Baker, PhD, professor of genetics at Stanford. "Each animal has come up with their

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Study: Absence of protein halts brain cancer growth

By Erin Digitale

Michelle Monje

The growth of certain aggressive brain tumors can be halted by cutting off their access to a signaling molecule produced by the brain's nerve cells, according to a new study by researchers at the School of Medicine.

When the signaling molecule neuroligin-3 was absent, or when its signal was interrupted with medication, human cancers called high-grade gliomas could not spread in the brains of mice, the researchers found.

The study was published online Sept. 20 in *Nature*. Graduate student Humsa Venkatesh is the study's lead author.

"We thought that when we put glioma cells into a mouse brain that was neuroligin-3 deficient, that might decrease tumor growth to some measurable extent. What we found was really startling to us: For several months, these brain tumors simply didn't grow," said Michelle Monje, MD, PhD, assistant professor of neurology and senior author of the study. The findings suggest that interrupting the

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Study: DACA eligibility for mothers improves children's mental health

By Mary Duan

Children of undocumented parents face high levels of anxiety, a natural result of living with the fear and uncertainty that a parent could be targeted for deportation, swept up by Immigration and Customs Enforcement, and sent back to his or her country of origin. Lack of documentation causes many such families to live in the shadows, attempting to stay off government radar while remaining in the United States.

A team of researchers led by the Stanford Immigration Policy Lab set out to examine if some measure of protection for undocumented mothers could result in less anxiety — and lessen the need for mental health treatment — for their children. Their study shows that U.S.-born children of mothers eligible for Deferred Action for Childhood Arrivals program suffer from lower rates of anxiety and adjustment disorders when compared with U.S.-born children of undocumented mothers ineligible for DACA.

The study was published Sept. 8 in *Science*. Lead authorship is shared by Jens Hainmueller, PhD, professor of political science at Stanford and co-director of the Stanford Immigration Policy Lab; Duncan Lawrence, PhD, executive director of the lab; and postdoctoral scholar Linna Marten, PhD. The senior author is David Laitin, PhD, professor of political science and co-director of the lab.

President Donald Trump recently announced plans to rescind DACA, a program enacted in 2012 that allows some people who entered the U.S. illegally as minors to receive renewable two-year periods of deferred action from deportation and eligibility for a work permit.

DACA has protected nearly 800,000 undocumented immigrants brought here as children. But the researchers hope policymakers will use a broader calculus in future decision-making and take into account the positive impacts DACA has on recipients' families — and the negative impacts that could result from wholesale deportation.

Hainmueller said he and his colleagues were motivated by the lack of evidence that exists on the undocumented population in the United States. They chose to examine DACA, he said, because it's the most significant immigration policy of the last two decades.

"There are a lot of beliefs about policies, but not a lot of evidence on how policies impact the undocumented and the communities in which they live," Hainmueller said. Moreover, little has been written about how DACA protections impact a recipient's family, with most research and policy focusing instead on the individual recipients, including studies that show DACA recipients have higher rates of employment and improved health outcomes.

"We decided to look at the intergenerational effects of DACA and whether there were spillovers on the protections of parents into the lives of their kids. That was the motivation — there had been no research on the intergenerational effects of DACA," Hainmueller said.

Fernando Mendoza, MD, a professor of pediatrics at Stanford and co-author of the study, pointed to the loss of a parent — whether by death, divorce or deportation — as one of the greatest stresses of children.

"However, in the case of deportation, the level of stress is heightened by the uncertainty of the event. Think about a young child going to school one day and returning home and not finding their mother. Or having the father leave in the morning, and always thinking, 'Will this be the last time I see him?'" Mendoza said. "This is the current status of 4 million children who have one undocumented parent. This is the stress and uncertainty that DACA was able to relieve."

Digging into the data

The research team used claims data from Oregon's Emergency Medicaid program, which is heavily used by undocumented immigrant mothers. The data on births spanned 2003-15; because the children were born in Oregon, and thus are U.S. citizens, those children became eligible for traditional Medicaid.

In all, they identified 5,563 mothers born between 1980 and 1982 who were covered by Emergency Medicaid and gave birth to 8,424 children during 2003-15. Then they tracked the children's mental health outcomes using their Medicaid claims.

Researchers further narrowed in on adjustment and anxiety disorders, theorizing that children may be stressed by the uncertainty of their parents' immigration status.

What they found is that mothers' DACA eligibility significantly decreased adjustment and anxiety disorder diagnoses among their children and that parents' unauthorized status is a significant barrier to normal child development and perpetuates health inequalities.

"We found that before DACA was implemented, the rates of mental health diagnosis were exactly the same; but in the post-DACA period, mothers started to benefit from protection and the rates of adjustment and anxiety disorders dropped by half," Hainmueller said.

"When you consider the social determinants of mental health, there are a lot of things that are hard to change, but here we have an instance of a dramatic improvement in the mental health of those kids. You can, through a law, get a dramatic improvement in health. And unlike poverty, that's something uniquely changeable," he said.

But just as a law helped change mental health outcomes for kids in this study in a positive way, so too can an absence or reversal of the law change outcomes in a negative way.

"If it were to be reversed, those gains would quickly evaporate and maybe reverse and these parents would be back in the shadows," Hainmueller said.

DALE LEMMERICK

Stanford medical students show their support for the Deferred Action for Childhood Arrivals program during a Sept. 14 rally at the Li Ka Shing Center for Learning & Knowledge.

Next steps

The researchers are trying to obtain similar mental health data of children of DACA recipients in California and New York. Also, as a follow-up to the research based on data from Oregon, the team has an ongoing effort to interview families impacted by DACA. So far, they've completed 25 interviews.

"One of the things the study can't do, with quantitative data, is determine what's leading to the dramatic improvement we see," Hainmueller said. "We don't know if it's job security, reduced stress because there's less anxiety, but hopefully that will come out in more qualitative interviews."

The study's results imply that expanding deferred action to the millions of unauthorized immigrant parents who do not meet the current DACA eligibility criteria could further promote the health and well-being of this next generation of American citizens. And the study states it's also reasonable to expect that permanent legal status or a pathway to citizenship would have an equal, if not greater, effect in improving children's health.

Other Stanford co-authors of the study are postdoctoral scholar Lucila Figueroa, PhD; Michael Hotard, program manager of the Immigration Policy Lab; and Tomás Jiménez, PhD, associate professor of sociology.

Researchers from Uppsala University, Northwestern University and Oregon Health & Science University also contributed to the work.

The study was supported by the Russell Sage Foundation and the Ford Foundation. **ISM**

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
3172 Porter Drive
Palo Alto, CA 94304
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

Paul Costello
Chief communications officer
Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

Send letters, comments and story ideas to John Sanford at 723-8309 or at jsanford@stanford.edu. Please also contact him to receive an e-mail version of *Inside Stanford Medicine*.

STANFORD MEDICINE

Spectrum debuts revamped clinical research website

Stanford University recently completed a major update to the Spectrum website, a collection of resources that assists researchers with the complex process of conducting clinical and translational research. Managed by Spectrum, which is the Stanford Center for Clinical and Translational Research and Education, the website is part of an ongoing effort to streamline this type of research across the university.

Enhancements to the website include:

- Improved site navigation and content organization.
- A unified page for research-related forms, documents, budget workbooks, pricelists and templates.
- Links to university-wide resources and consulting services for the design and conduct of research.
- Consolidated information on funding and educational opportunities offered by Spectrum.
- A dashboard for viewing all shared scientific core facilities across the university.
- A portal to the expanded services in the Clinical Trial Research Unit and Spectrum Biobank.
- Information on Spectrum's recently established Clinical Research Quality office, which provides advice on procedures, audits and the ClinicalTrials.gov registry.
- Updates that reflect Spectrum's recent organizational and leadership changes.

To try out the new Spectrum website, visit: http://med.stanford.edu/spectrum.html. To ask questions or provide feedback, contact spectrum_webmaster@lists.stanford.edu. **ISM**

Researchers team up to reduce pollution and improve health

By Rob Jordan

Stephen Luby's epiphany came to him 30,000 feet up in the air. The Stanford epidemiologist was flying over India when he realized the view from his window seat was adequate to identify brick kilns on the ground below. The insight was startling for its potential to shed light on an environmental nightmare that kills thousands of people every year.

Luby, MD, professor of medicine, and a team of Stanford researchers including political scientist Francis Fukuyama, PhD, and geophysicist Howard Zebker, PhD, are following up on Luby's insight to revolutionize brickmaking in South Asia, an industry that burns coal, biomass and even tires to dry hand-molded clay into the ubiquitous building material. Brick kilns across South Asia have a global warming impact equivalent to that of all passenger cars in the United States, and air pollution from these kilns kills tens of thousands of people each year as a result of respiratory and cardiovascular disease, according to Luby.

Starting in Bangladesh, the novel collaboration is working to measure kilns' health effects and incentivize kiln owners to switch to cleaner technologies.

"We're doing something completely novel here," Luby said.

First find the kilns

Before they could reach out to kiln owners, the researchers had to figure out the number and location of kilns, which are poorly regulated and tracked. That's where Luby's Jet Airways flight comes in.

"I got to thinking: Well, wait a minute, if I can do this sitting in a plane, we must be able by remote satellite to detect [kilns] as well," Luby said of his aha moment.

Stephen Luby

When Luby's plane touched down, he looked up Stanford satellite data experts. He found Zebker, a professor of electrical engineering and geophysics and an authority on developing space-borne radar systems and using remote sensing data to study earthquakes, volcanoes, polar ice movements and other phenomena. "This being Stanford, I can send him an email, and he says 'Yeah, sure, let's have coffee.'" Luby looped in Fukuyama, a senior fellow at the Freeman Spogli Institute for International Studies, to help him understand related governance issues and formulate a politically effective message of change.

One form this message will take is a public website allowing people to locate information about kilns in their area and to learn ways of nudging kiln owners toward making their operations more efficient and profitable. Site users will be able to pinpoint kilns that violate ordinances on proximity to communities and on design standards, among others, and join a larger discussion among public and private sector stakeholders.

"It won't just be an outdated report nobody sees," Luby said.

Crucial to the planned website — and the entire initiative — is the Sentinel 1 satellite launched by the European Space Agency in 2015. It provides publicly available images of Earth at a resolution about the size of a racquetball court (30 by 30 feet). Armed with that data and GPS locations of kilns found by ground teams, electrical engineering graduate student Abhilash Sunder Raj developed a model that understands what kilns look like from space. Sunder Raj adjusted his algorithm to account for seasonality (kilns don't run in the rainy season from November to March) and to avoid false positives, such as household fires and furnaces. The model worked so well that it even found kilns the ground team had missed.

"We are able to find these needles in a haystack very, very accurately," Sunder Raj said.

Serious health risk

They may look innocuous from space, but kilns are outsized threats on the ground. In Bangladesh, a single brick kiln puts out up to 105,822 pounds of carbon monoxide in one season. Multiply that by the country's 8,000 or more kilns, and you have a catastrophe for health and global warming. Researchers in Bangladesh have found dangerous airborne particulates at average levels more than 90 times greater than World Health Organization-recommended levels. The result: hundreds of thousands of people who live downwind from kilns are at elevated risk for cardiovascular and respiratory diseases.

Although the kilns are clearly a health risk, there's not much good data about the magnitude of the problem. Alex Yu, MD, a postdoctoral scholar in infectious disease, is trying to fill in those gaps and learn whether other sources of pollution contribute to health problems to an extent that even if brick kilns were less polluting, the health issues would continue. He is comparing rates of asthma, pneumonia and carbon monoxide, among other air-related illnesses, in villages with and without kilns.

SCOTT RANDALL / FLICKR

In Bangladesh, a single brick kiln emits as much as 105,822 pounds of carbon monoxide in one season.

"There are chimney stacks everywhere pouring out black smog," Yu said of the dystopian landscape he witnessed on the outskirts of Dhaka, Bangladesh's capital city. "You walk one block and your body is covered by a thin layer of soot."

In addition to contaminating air, the kilns degrade soil around them as workers dig it up to be made into the clay that will be molded, heated and dried into bricks. Runoff from stripped patches of land damages the fertility of surrounding cropland, making it harder to grow food and compounding the kilns' health effects, Yu said.

Incentives for change

Shifting the brick-making paradigm in Bangledesh and other countries that rely on the polluting kilns will require shifting incentives. Leo Kirby, a graduate student in the International Policy Study program and a research assistant to Fukuyama, is looking at how to most effectively align the interests of stakeholder groups in Bangladesh and how to identify effective approaches to behavior change in a country where the rule of law has limited reach.

"It's a great example of the challenges of changing policy in an environment of weak governance," Kirby said. "Existing regulations are imperfectly enforced at best. So, to change behavior, you have to change the incentive structures."

Kirby's interviews with brick kiln owners, international nongovernmental organizations and various environmental and community organizations will serve as the basis for a case study for a policy reform training program Fukuyama runs for mid-career public officials in developing countries.

Nina Brooks, a doctoral candidate in the Emmett Interdisciplinary Program in Environment and Resources, will talk with kiln owners to better understand what constrains decisions to adopt improved efficiency. The Stanford team is working with Greentech Knowledge Solutions, a Delhi-based leader in improving brick kiln efficiency.

Luby is approaching the climate community to help support the transformation of the brick kiln sector in Bangladesh and, ultimately, across South Asia. He said the improvements in efficiency will pay for themselves, but stakeholders will need support to achieve this more favorable equilibrium.

Luby is also a senior fellow at the Stanford Woods Institute for the Environment and the Freeman Spogli Institute for International Studies, and director of research at the Center for Innovation in Global Health.

Fukuyama is also the Olivier Nomellini Senior Fellow and Mosbacher Director at the Center on Democracy, Development and the Rule of Law in the Freeman Spogli Institute.

The research is supported by the Stanford Woods Institute's Environmental Venture Projects program and the Stanford Food Allergy Center Fund. ISM

COURTESY OF STANFORD MEDICINE X

A father's quest to help his daughter

With her father beside her whispering encouragement, Lorelei Hoenen, a 6-year-old with a blonde ponytail, looked out across the silent crowd at Stanford Medicine X on Sept. 15. "Last year, I got very sick," she said.

She had been struck by acute flaccid myelitis, a rare polio-like illness. She got better, but her left arm remained paralyzed. Bodo Hoenen, her father, set out to create a mechanical assistive arm for his daughter. By posting videos of Lorelei's story, family members enlisted the help of experts across the world, and published their efforts online to help other families.

To everyone's surprise, Lorelei eventually recovered the use of her arm. But Bodo said the time spent working on the robotic arm wasn't wasted. "It provided us tangible hope," he said. For more stories from the conference, which focused on patient-centered medicine and emerging health care technology, visit http://scopeblog.stanford.edu. ISM

First-generation MD, grad students and their mentors honored

By Tracie White

As the first in his family to attend college, Alvaro Amorin was forced to tackle many challenges on his own. His parents, who immigrated to the United States from Peru when he was 12, didn't have the experience needed to help answer his many questions about college, starting with how to apply.

"I wasn't really going to go to college," said Amorin, now a second-year medical student at Stanford. "My parents didn't know anything about enrolling."

"I didn't know what the SATs were," said his friend and fellow second-year medical student Hector Martinez, also the first in his family to attend college.

Amorin and Martinez, who took part in the medical school's First Generation Mentorship Program, were among the mentees and mentors honored at the end of the yearlong program at a ceremony Sept. 11 in the Arrillaga Alumni Center.

Designed to pair first-generation medical students and graduate students in the biosciences with mentors who were themselves once first-generation medical or graduate students, the program paired 18 students this past year. Their mentors included faculty, alumni and biotechnology executives. The program defines first-generation students as those who are first in their families to go to college or graduate school, or those who were the first in their families to be born in the United States,

In its just-completed second year, the program not only matched mentors and mentees, it added seminars on such topics as "social belonging" and the "imposter syndrome" — a common feeling among students at elite universities that someone made a mistake letting them in, and they really don't belong. The mentees also benefitted from connecting with mentors in different fields through various events, including a panel discussion

"This program helps the Stanford Medicine first-year students approach their graduate school journey with the support of a community of alumni, faculty and staff partners," said Mijiza Sanchez, EdD, associate dean for medical student affairs and founding director of the program.

The program was initially funded in 2016 with seed money from Stanford Associates, an organization of Stanford alumni.

"I'm first-gen, and I know from my own experiences when you don't have someone who has gone through college there for guidance, it's hard to navigate, especially at a place like Stanford," Sanchez said. "My parents are immigrants from the West Indies. I didn't have a road map laid out for me. But I have had many extraordinary mentors who helped me direct my path."

STEVE FISCH

STEVE FISCH

Mijiza Sanchez (left), founding director of the First Generation Mentorship Program, and Stanford President Marc Tessier-Lavigne speak at the ceremony, which was held at the Arrillaga Alumni Center.

Stanford president's story

Marc Tessier-Lavigne, PhD, president of Stanford University, spoke to the program's mentors and mentees, telling the story of his own challenges as the first in his family to attend college.

"My parents didn't go to college. My father didn't graduate from high school," said Tessier-Lavigne, a neuroscientist and former biotechnology executive and Rhodes Scholar.

Born in Canada, Tessier-Lavigne attended McGill University as an undergraduate. He said mentorship played a key role in his college success. His parents, who were in the military and moved the family from the province of Ontario to London and Brussels, always supported his desire to go to college, but they couldn't advise him on how to achieve his goals, he said.

STEVE FISCH

Alvaro Amorin, who immigrated to the United States from Peru, completed the medical school's yearlong First Generation Mentorship Program.

"Most of us want to turn to our parents for advice," he said. Which he did. He asked his parents myriad questions about college, like seeking advice on what major to choose, but they just didn't have the experience to answer.

"Mostly what they said was, 'I'm sure you'll make the right decision,'" he said. "They couldn't tell me things like, 'Maybe you should get an internship in the summer.'

"For me, I always wanted to be a scientist," he continued. "As an undergraduate, I didn't know what it would entail to become a scientist. I had never met a scientist before I went to college."

Instead of luck, a program

Much of his success in connecting with great mentors was based on luck, he said.

"I'm thrilled we have a program like this at Stanford," **See PROGRAM, page 8**

Book compiles evidence that climate change is making us sick

By Tracie White

In 2008, Jay Lemery, MD, an emergency physician in Colorado, read a commentary about the effects of global climate change on human health. The author was Paul Auerbach, MD, professor of emergency medicine at Stanford and one of the world's leading authorities on wilderness medicine.

Published in the *Journal of the American Medical Association*, the article caught Lemery's attention.

"What I immediately thought was we need to have a physician movement around this," said Lemery, associate professor of emergency medicine at the University of Colorado and section chief of wilderness and environmental medicine.

Now, a decade later, Lemery has co-authored a book with Auerbach that delves into the growing health issues touched upon in that 2008 article — the countless, frightening ways that climate change is increasing allergens, creating toxic algal blooms, inducing heat stress, causing air degradation, and creating water and food insecurity. The book, *Enviromedics: The Impact of Climate Change on Human Health*, not only calls on physicians, but everyone on the planet, to take note. The book is scheduled to be published in October.

Paul Auerbach

Trying to hasten a 'reasonable response'

"We don't see the world moving fast enough to protect the planet, so perhaps by moving the discussion to human health we can hasten some sort of reasonable response," Auerbach said. "Hurricanes Harvey and Irma are already causing a considerable health impact, such as floodwaters contaminated with bacteria and toxins, drowning deaths, disruption of essential medical care and even floating fire ant colonies."

Lemery said, "On the hottest day of the year, patients come to the ER with heart attacks, COPD [chronic obstructive pulmonary disease] exacerbations and diabetes complications. If you do what we do, it's not that hard to see the link between global warming and human illness."

"We don't see the world moving fast enough to protect the planet."

The book lays out in disturbing detail how human afflictions are proliferating due to man-made environmental change, and it's likely to only get worse. More intense heat waves are killing the sick and the elderly; increasing air degradation sends asthma sufferers into serious and sometimes deadly attacks; hotter temperatures are spreading mosquito-borne diseases. The authors warn that if nothing is done to curtail climate change, it will do much more than cause the extinction of polar bears: It may threaten humanity. By bringing together the many risks to human health in one book, the authors hope to propel people into action.

"People may have heard scattered comments about global climate change, but I don't think they've looked at the issue as an aggregate whole," Auerbach said. "It's time for everyone to realize that it could conceivably become now or never on this issue because there soon may be much more environmental chaos and human suffering."

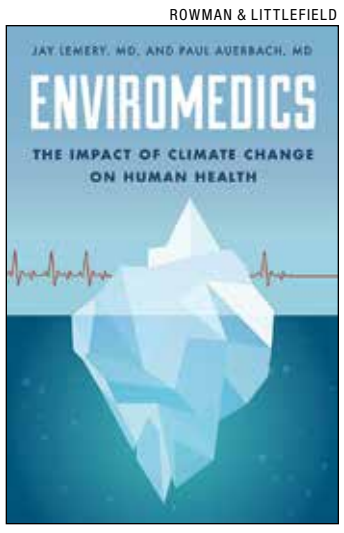
No one is immune

The book is grounded in the overwhelming scientific evidence of global warming. To write it, the authors conducted extensive research, as well as called upon their firsthand experiences with cases linked to climate change. The following are a few examples from the book that illustrate how no one is immune from the health effects of the phenomenon:

• A warmer world with greater weather extremes and increased atmospheric turbulence that degrades air quality will affect more people and increase the severity and number of asthma attacks. The book uses the fictional story of Sandra, a young woman with asthma in the South Bronx, who almost dies during a heat wave as temperatures soar toward 110 degrees.

• Extreme weather causes more severe storms and flooding, magnifying the ubiquitous problem of sewage overflow. The lack of access to clean water has been linked to outbreaks of such illnesses as cholera, hepatitis A, ringworm and scabies. The book introduces us to Andrew, a fictional character who starts itching violently after wading in a polluted river near his home. The doctor diagnoses what is now a common household disorder contracted from dirty water: scabies. The minuscule human scabies mite completes its entire life cycle on the skin of humans and, untreated, might live there for years.

ROWMAN & LITTLEFIELD



• The book enumerates the ways in which drought can force people to abandon safe practices and use whatever resources are available. In Tanzania and Mozambique, drought conditions were associated with outbreaks of konzo, a devastating neurological disease that causes irreversible paralysis. A report from Brazil in 1996 cited more than 50 deaths from liver failure when local cyanotoxin-contaminated water was unknowingly used for kidney dialysis.

The two physicians have treated patients with most of the illnesses and conditions described in the book. Global warming, as far as they know, is not causing new disorders, but rather spreading them and making them worse. "This is an inventory of what happens when our environment goes haywire, and all the checks and balances of an ecosystem are gone," Lemery said. "We should all pause. We should all worry." **ISM**

5 QUESTIONS

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

Marcia Stefanick on better medicine for women

The dearth of clinical research that accounts for both the sex and gender of patients often makes it difficult for doctors to diagnose and assess treatments that would most benefit women, but the problem goes beyond that, according to Marcia Stefanick, PhD, professor of medicine at the Stanford Prevention Research Center.

She believes a deeper, overall understanding of sex and gender differences in research and treatment will result in more inclusive, and more precise, medicine for everyone.

"The system can be blind to gender bias; some disorders are considered 'a man's or 'a woman's, even when both sexes suffer from them," Stefanick noted in an article she wrote for the September issue of Scientific American. *"Doctors often fail to diagnose stereotypical 'male' conditions in women, and vice versa, until the condition has become dangerous."*

As director and co-founder of the Stanford Women and Sex Differences in Medicine Center, Stefanick aims to raise awareness of the issue with the goal of improving health outcomes and care for everyone across the life course and gender spectrum. The center offers seed grants to encourage researchers to emphasize sex and gender in their work; provides a range of courses on sex, gender and sexuality for medical, graduate and undergraduate students; and organizes symposiums on women's health and sex differences for the broader university community.

Stefanick pointed to work by Londa Schiebinger, PhD, a Stanford professor of history of science who has developed a project to provide methods of sex and gender analysis for scientists and engineers. Stefanick said Schiebinger and her colleagues are pilot-testing a survey tool that was designed to measure gender and hope it will replace a scale created at Stanford in the 1970s that was based on gender norms of that era.

Writer Patricia Hannon recently asked Stefanick to discuss her work to make medical research and treatment more inclusive.

1 What do you consider the biggest challenge to ensuring that sex and gender are routinely considered as variables in biological research?

STEFANICK: There is a systematic lack of recognition, and therefore interest, among basic researchers of the possible role of sex in the questions they are pursuing, and also a general lack of understanding of what "gender" is and that it is not synonymous with "sex."

It's crucial, for example, that the differences in the sex of chromosomes or the differences in hormone-producing glands — and hormone levels — be considered in any clinical research so that it and any resulting treatment represent both men and women.

New diagnostic tests address the divide in some research, especially with regard to identifying and treating heart disease in women, but prevention and treatment guidelines are still based primarily on research that was mostly conducted on males.

Marcia Stefanick

2 What areas of medicine can most quickly benefit from a shift in focus to improve standards of care for women?

STEFANICK: Raising awareness of sex differences in immunology and cancer would be of immediate benefit to women, but would also benefit a large proportion of men.

It is worth pointing out that cardiovascular medicine has been a leader in recognizing the importance of differences between women and men, particularly younger women versus their male counterparts, in specific conditions, symptoms, diagnoses and optimal treatments. Yet a large proportion of people, including physicians, still consider heart disease a "man's disease" and do not apply the best prevention or treatment approaches for women to their female patients.

3 You say that considering gender and sex in both research and treatment benefits everyone. How does it benefit men, and why do you think this is especially important now?

STEFANICK: The more we learn about how treatments affect women differently from men, the more we also learn about the range of biological implications among men and women, as well as the "spectrum" of biological sex rather than the contrasts and differences between them.

For example, 15 percent of women who were prescribed what was at first considered the standard dose of Ambien experienced driving impairment eight hours after taking it. In addition, 3 percent of the men reported the same side effect when taking the then-standard dose of the widely prescribed sleeping medication. The side effect alerted physicians to the need to lower the dose in women, but it also indicates a need to consider how doses apply to men, as well.

The same principle applies to understanding that few diseases affect only men or only women. So the more we learn about diseases that affect one sex predominantly, the more we should learn about detecting and treating that disease in the opposite sex.

4 You are obviously passionate about making medicine more inclusive. What drives you to be such a strong advocate for change?

STEFANICK: Most scientists want to have precise and accurate information about whatever they are studying, and I don't believe we can have this without seeking a more comprehensive understanding of sex and gender than our current, biased knowledge base.

There is plenty of evidence that men and women differ in many ways beyond reproductive function, and yet we tend to offer a one-size-fits-all medical approach. On the other hand, our societal biases overemphasize sex and gender differences in many domains that lead to biased medical practice, which is also harmful.

But beyond medicine, understanding a fuller range and spectrum of male to female biology would give us more insight into basic biology.

5 Do you have suggestions for how women can advocate for themselves in interactions with physicians and others involved in their care?

STEFANICK: Ask physicians questions about what evidence there is in women (and/or whatever age group they fall into, or if pregnant) for any diagnostic test or treatment they are about to conduct or prescribe. This would raise awareness among physicians that they probably never learned this in medical school or pursued these questions on their own.

In a nutshell, physicians assume that what they've learned is appropriate for most of their patients. In fact, there may be little to no information about gender differences for many of the drugs and treatments they prescribe. Physicians should think about their oath to "do no harm" in the context of what they know or do not know about how they are managing the health care of the full range of patients in their practice, particularly women, who have often not been included in clinical studies or who have not been studied across the range of their reproductive phases.

We need to raise awareness of the fact that we are not providing optimal care and may even be harming half of our patients, and also that we have many biases that lead to wrong assumptions which may be thwarting our progress in understanding basic biology. **ISM**

After years of working through pain, acceptance to a top college

By Samantha Dorman

Hari Suresh, 20, of Fremont is embarking on his freshman year at UC-Davis, where classes begin today. Yet his journey to college was perhaps a longer, more complicated path than it was for most high school teens.

Suresh not only fought through years of illness and chronic pain but also to get the education he needed so he could go on to college. Luckily, he and his family found help through an advocacy program and integrated complex care team at Lucile Packard Children's Hospital Stanford, to which he gives credit, along with his dutiful persistence, for making it possible to realize his goal.

In 2008, Suresh was diagnosed at Packard Children's with juvenile arthritis, which caused painful joint inflammation. During his junior year of high school, when most of his peers were gearing up to send out college applications, he was diagnosed with Crohn's colitis, a chronic condition that causes inflammation in the walls of the digestive tract and large intestine. Painful flare-ups are often unpredictable, and symptoms include heavy cramping and frequent diarrhea.

Suresh's gastroenterologist, William Berquist, MD, professor of pediatric gastroenterology at the School of Medicine, recalled, "I began seeing Hari over four years ago at a point which his symptoms were significant, his body had difficulty maintaining good nutritional status and he was also dealing with sleep issues."

That was the beginning of a two-year interruption in his schooling, missing graduation with his class and missing the connection to friends and high school life. Suresh wondered whether his life would ever be "normal" again.

A straight-A student

Suresh had always excelled in school. He was a straight-A student who enjoyed scholastics.

"School had always been a huge part of my life, and to have that removed for that period was very distressing," he said. "It was difficult to be cut off from my peers over that time. I felt isolated."

During that time, Suresh found support in his care team in the Pediatric Pain Management Clinic at Packard Children's. Here, Suresh went through the intensive pain program, which involved a month of seven- to eight-hour days of physical and occupational therapies and pain psychology that would help increase his endurance and get him back into school. At the clinic, he also encountered other young people who had chronic illnesses and similar experiences.

"For the first time in a long time, I felt a sense of camaraderie with my peers," Suresh said. "Like I was just 'one of the guys,' so to speak."

Rashmi Bhandari, PhD, a pain psychologist in the clinic who has provided

COURTESY OF THE SURESH FAMILY

Hari Suresh with Jeanne Kane, who supervises the Hospital Educational Advocacy Liaisons program at Packard Children's Hospital.

mental health support to Suresh and his family since the beginning of his complex medical journey, emphasized how chronic pain and illness can impact a young person's ability to develop independence, confidence and social competence, and heighten psychological vulnerability.

"The natural reaction to pain is learning how to avoid it, and pain-avoidant behaviors lead to significant functional impairment," said Bhandari, clinical associate professor of anesthesiology, perioperative and pain medicine at the School of Medicine.

Chronic pain and illness interfere with a child's trajectory in school, often leading to frequent absences; difficulties with focus, performance and learning; and frequently feeling behind and stressed out. Bhandari described it as a vicious cycle that leads to social isolation and increased stress. What's more, "stress and isolation exacerbate the experience of pain," she said.

'Challenge for the entire family'

"An interruption in a young person's 'normal' academic and social life due to chronic medical illness presents a major challenge for the entire family," said Jeanne Kane, MA, supervisor for Packard Children's HEAL program. HEAL stands for Hospital Educational Advocacy Liaisons, and its mission is to enable families with medically fragile children experience success in learning despite limitations imposed by their medical condition.

"We know that life returning to 'normal' activities, like education, is critical for a child's optimal adjustment," said Kane. "And parents and children often face new obstacles when the child returns to school."

One of those obstacles was securing educational accommodations from his school. His frequent **See PAIN, page 8**

Optics

continued from page 1

and I finally told him, 'This guy is never going to be able to fix me; he wears glasses!'

"My father said, 'Well, you know, sometimes people decide to base their careers on things related to problems they themselves have experienced.'" Dubra's grandfather, a cardiologist in Uruguay, had chosen his career in response to his own heart problems. Then and there, Dubra decided to devote his life to learning more about the eyes and how they work. But his early plan of attending medical school was thwarted when his middle school biology teacher brought a dead fish to class for dissection.

"Immediately I knew, 'No, I can't go into medicine,'" Dubra recalled. So he chose a different but related path important to vision: physics.

How vision works

The fundamentals of vision are this: Light enters the eye, which is roughly the size and shape of a ping-pong ball, through a thin layer of tissue called the cornea. The cornea begins the process of focusing the light as it enters through a hole in the iris called the pupil. Immediately behind the pupil, the light passes through a lens that serves to focus the light onto a layer of light-sensing cells at the back of the eye — the retina. The optic nerve then transmits signals from cells in the retina to the brain to be decoded as visual images.

The retina lines the inner three-quarters of the eye; laid flat it would be a little bigger than a quarter. It's peppered with cone cells, which discern the colors red, green and blue; rod cells which allow us to see in dim light, but don't perceive color; and retinal ganglion cells, which connect the rod and cone cells to the brain via the optic nerve. Humans have about 120 million tiny rod cells and about 6 million larger cone cells.

Diseases that affect vision can occur in the cornea, lens, retina, optic nerve or even the brain. But although the cornea and lens can be replaced with donated or synthetic tissues, the retina and the optic nerve are much more precious.

"The retina is a direct outgrowth of the brain," said Dubra. "Almost all the cells in the retina are neurons. And, like neurons in the brain and spinal cord, when they die, they don't get replaced. That cell loss is permanent."

It's also insidious. The first stages of many retinal diseases are gradual and unnoticeable; most people don't discover any vision changes until a critical mass of cells are lost. And although some gene therapy approaches have shown promise in replacing faulty or missing copies of proteins that keep the retina healthy, the technique falls flat when the cells themselves are missing.

"You can't cure cells that aren't there," Dubra said. "That's why diagnosing these diseases as early as possible is the goal of every ophthalmologist. But by the time a person notices vision impairment, thousands of cells are likely to have died."

"Although many of these diseases are currently incurable," he added, "in some cases there are drugs that can slow their progress. If we could diagnose them early, and treat them throughout a person's life, vision loss that significantly affects a person's quality of life could be prevented. Ideally, we would also be able to monitor whether a chosen therapy is working, or if a different therapy or drug should be tried."

So how can we monitor individual rod and cone cells in the retina? It might not seem like a big deal. After all, we routinely image cells outside the body using high-powered light or even electron microscopy. But Dubra and his colleagues need to visualize the living cells of retina. This presents particular optical challenges.

All of us see objects by collecting, focusing and interpreting the patterns of light that bounce off them and reach our eye. Our brains learn how to compensate for the vagaries of our individual eye structure: They can determine that one wavy pattern of light reaching our retinas is our family dog waiting lovingly by the back door and that another is a mountain lion lurking in the bushes along our evening jogging route. Sometimes this interpretation is improved with the help of eyeglasses or contact lenses to correct for common deformities.

From outer space to the eye

When it comes to looking at the retina itself, however, the tables are turned. Now the clinician is trying to interpret light waves bouncing off the patient's retina as they retrace their steps out of the eye, passing through the lens and cornea and even the veil of protective tears that cover the eye's surface. Each of these obstacles can jumble the waves of reflected light and make fine details difficult to discern.What's more, each patient is unique, from right eye to left eye and even from moment to moment as the eye is repeatedly wetted with each blink.

These complications could be avoided if the retina could be removed from the eye and examined directly in the absence of tears, cornea, lens, etc. But that's obviously not the preferred approach for a patient who ever wants to see again.

BRIAN SMALE

The adaptive optics machines are essentially "a cross between a telescope, a microscope and a camera," according to Dubra.

In short, looking at the retina at any level of fine detail is challenging. Unless, that is, you're familiar with outer space and international intrigue.

Adaptive optics arose as a result of the Cold War, when U.S. military specialists were eager to track Russian spy satellites orbiting high above the Earth. But atmospheric distortion of the light reflected from the satellites limited what telescopes on the ground could see. This distortion is the same reason stars appear to twinkle.

"Light waves from those stars travel many light years to reach Earth, and then at the last small fraction of a second they enter our atmosphere," Dubra said. "Pockets of hot and cold air act as lenses that bend these rays of that light and make the images of the stars appear blurry or flickering."

The effect is similar to the visual distortions we've all noticed when looking down a long, empty stretch of highway on a hot day, or gazing at someone across a bonfire. The air itself appears wavy and details are difficult to pick out.

"Now imagine if you had a magical device that could intercept these distorted light waves and correct them," Dubra said . American astronomer Horace Babcock, PhD, came up with just such an approach in 1953 when he suggested bouncing the distorted waves off a deformable mirror. Linking the mirror to a device that could sense the distortion would then allow the mirror to repeatedly and quickly adjust as necessary to realign the light waves and re-create a sharp, visible image.

The idea worked, and military researchers spent decades optimizing this "adaptive optics" technology as a way to better track Russian spy satellites far above the Earth.

When the Cold War ended in 1991 with the fall of the Soviet Union, the military declassified their work on adaptive optics, and medical researchers quickly realized the technique's promise for peering into the inner space of the human eye. In 1997, researchers at the University of Rochester's Center for Visual Science — including Junzhong Liang, PhD; David Williams, PhD; and Donald Miller, PhD — published the first paper showing that adaptive optics could allow them to see individual cone cells with "unprecedented resolution."

'I had to leave'

At about the same time, Dubra, who was finishing up his undergraduate studies in physics in Uruguay, was coming to a bleak realization of his own. "At some point, I came to understand that we were never going to study the eye here. There were just no researchers in this country specializing in the physics of vision. So I had to leave."

After finishing his master's degree in 2000, Dubra headed to the United Kingdom to complete a doctorate and postdoctoral studies at the Blackett Laboratory in Imperial College London, where he designed and built a machine to study the topography of the film of tears that cover the surface of the eye with each blink.

In 2006, he packed his bags to join Williams' laboratory in Rochester. "David's team pioneered adaptive optics for retinal imaging," Dubra said. "So there was a unique opportunity to learn about vision science while also further advancing the imaging technology."

In 2011, Dubra, then an assistant professor of ophthalmology at Rochester, hit upon a way to change the three-dimensional orientation of the series of imaging mirrors in such a way that it became possible to visualize not just cone cells, but also the much smaller, and more numerous, rod cells. This was a major technical achievement.

"We and others had thought that these cells were far too small for us to see in the living eye," Dubra said. "But many diseases start in these rod cells and then propagate to other cell types. So imaging them is very important."

If the human eye is about the size of a ping-pong ball, the machines that Dubra and his colleagues build are roughly the size and shape of a thick ping-pong table. The patient sits at the end of one of the longer sides and aligns an eye with the machine by resting their chin on a support and peering into a box built on top of the table, which looks somewhat like an old-style film camera with a photographer's hood. The retina is illuminated with light that enters the pupil of the eye; a series of mirrors and detectors housed under the protective cover correct, focus and capture the light waves leaving the patient's retina.

"Essentially this optical table is a cross between a telescope, a microscope and a camera," Dubra said. Though the construction doesn't appear especially noteworthy, the images it produces of the surface of the retina are nothing short of astounding. Whereas in the past researchers struggled to pick out landmarks in what would look like a uniformly gray circle crisscrossed with blurry, hardly visible blood vessels, it's now possible to clearly see individual red blood cells slowly pulsing their way, doubled over, through the tiniest retinal capillaries. Individual cone and rod cells seem to leap out at the viewer, and Dubra and his colleagues have even made progress toward identifying whether those cells are functional by, ironically, watching them twinkle like stars in response to flashes of colored light.

"Suddenly, it seems feasible to test a subset of cells in the retina, and maybe identify, for example, a handful of cells that are present but not functional," Dubra said. "Medically this is potentially very important. Gene therapy approaches, for example, rely on the presence of nonfunctional cells that could receive a corrected version of a faulty gene."

"There are two major leaps we have wanted to make in our research," he added. "We want to go from looking at structures in the retina on a relatively macroscopic scale to a microscopic scale — visualizing individual rods and cones, capillaries and blood cells in real time in a living eye. We're well on our way now, but there is still a fair amount of work to do. Secondly, and arguably more importantly, we'd like to find ways to monitor the function of these cells at a microscopic level. Maybe we can find a few thousand, or even a few hundred, cells that are not healthy. That may allow us to begin therapy before the patient experiences the 'point of no return,' or permanent, irreversible vision loss."

Testing new instruments

Dubra has not forgotten his ultimate goal to help those suffering from vision loss. In June, he and his lab members moved into the just-completed Mary M. and Sash A. Spencer Center for Vision Research, next-door to Stanford's Byers Eye Institute.

"In the new Spencer Center, we will develop and test the new generation of adaptive optics instruments in labs immediately adjacent to the rooms where they will be used to examine and diagnose patients," Dubra said. Instruments built by the Dubra lab are also being used, among other places, in the New York Eye and Ear Infirmary of Mount Sinai to study vascular diseases of the retina and at the University College London, the Medical College of Wisconsin and the University of Pennsylvania to identify good candidates for the world's first gene therapy trials aimed at rescuing damaged cone cells in the retina.

"Now we can tell how many cone cells a patient has before they enroll in the trials," Dubra said. "We can also follow patients over time to identify much more quickly those who might be benefiting from the treatment even before they experience functional changes in their vision."

The instruments also allow researchers to monitor the progress of blinding diseases in real time, rather than relying on cadaver tissue donated by people who had already lost their sight. This is particularly important for the numerous conditions that manifest only in a small number of individuals."We now have the opportunity to start to really understand and monitor the pathophysiology of these blinding diseases," Michaelides, of University College London, said. "Alf has a rare ability to interact with both scientists and clinicians to develop the technology necessary to help us help patients."

"I often think of that mom from my early days as a researcher in Rochester," Dubra said. "I wish I could talk to her now. I could outline the concrete ways that our work is moving the field forward in ways that will directly benefit people like her son." **ISM**

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

Wallaby

continued from page 1

own unique strategies for delivering the functions of the placenta that takes into account where they live, how many offspring they have and what they eat, for example. But the actual function is very well-conserved."

Baker shares senior authorship of the study, which was published online Sept. 12 in *eLife,* with Marilyn Renfree, PhD, a professor of zoology at the University of Melbourne. The lead author is Stanford graduate student Michael Guernsey.

A little wallaby

Guernsey and Baker studied the placenta of the tammar wallaby, which is native to Australia. To the marsupially naïve, it resembles a tiny kangaroo. Males weigh no more than 20 pounds and stand about 18 inches high. It forages hoppily by night. The tammar wallaby has a pregnancy that lasts a mere 26.5 days, after which the young climb into the pouch and nurse for the next 300 to 350 days as they complete their development.

The wallaby's placenta is deceptively simple.

"There are only two main tissue types," said Guernsey, "one responsible for nutrient distribution and one for respiration. We wanted to see which, if any, gene products found in the eutherian placenta are also in the marsupial placenta, and where they are expressed. Conversely, which eutherian markers might be missing?"

In contrast, the eutherian placenta is highly complex and comprises both maternal and fetal tissue.

Guernsey studied the RNA transcripts in the wallaby placenta and compared them with those found in eutherian mammals during various stages of fetal development. He found that the gene expression patterns in the marsupial placenta undergo dynamic, rapid changes during the last few days of the animals' short pregnancy, during which the placenta churns out proteins known to be important in the early stages of eutherian development.

"All of the wallabies' gene expression time points were most similar to those found in the early eutherian placenta," said Guernsey. "But where have the late functions of the eutherian placenta gone?"

Changes in the milk

A key might lie in the complex makeup of the animals' milk, the composition of which changes to meet the demands of the growing, pouch-bound youngster. It's so potent that placing an infant into the pouch of a mother who has been nursing a more developmentally enhanced baby causes the newcomer to beef up dramatically, increasing its head size and body weight and growing thicker fur than its age-matched peers.

> "Essentially, we're trying to understand how the placenta evolved in the first place."

To investigate the relationship between the marsupial placenta and the milk produced during lactation, the researchers homed in on 77 genes whose expression was shared among the tammar placenta, the eutherian placenta and the tammar mammary gland, but not the mouse mammary gland.

Many of the genes they identified were associated with nutrient transport. Another, known as GCM1, is a transcription factor essential to the function of eutherian placentas.

"This is the first documented expression of GCM1 outside the placenta in mammals," said Baker. "What we're learning is that the marsupial placenta functions much as it does in eutherians in the very early stages of development, but the expression of later-stage eutherian placental genes instead occurs in the mammary gland. So clearly although the placentas of humans, cows or mice are extraordinarily different from those of marsupials, the animals are fulfilling the same necessary functions in different ways."

STEVE FISCH

Julie Baker said that "although the placentas of humans, cows or mice are extraordinarily different from those of marsupials, the animals are fulfilling the same necessary functions in different ways."

"Essentially, we're trying to understand how the placenta evolved in the first place," said Guernsey. "It's a difficult question to answer. We're finding that we can begin to identify rudimentary placentas in other species as well, like lizards and fish. It will be really interesting to see whether, in this completely different evolutionary landscape, these functions are still conserved in ways that make sense for that animal."

Guillaume Cornelis, PhD, a postdoctoral scholar at Stanford, is also a co-author of the study.

The research was supported by a National Science Foundation, the Berry Foundation and the Australian Research Council.

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

Cancer

continued from page 1

neuroligin-3 signal could be a helpful strategy for controlling high-grade gliomas in human patients, Monje added.

High-grade gliomas are a group of deadly brain tumors that include adult glioblastoma, the brain cancer now affecting U.S. Sen. John McCain of Arizona; anaplastic oligodendroglioma; pediatric glioblastoma; and a pediatric tumor called diffuse intrinsic pontine glioma. Five-year survival rates are 60 percent for anaplastic oligodendroglioma, around 10 percent for adult and pediatric glioblastomas and virtually nonexistent for DIPG. New treatments are urgently needed.

Hijacking the normal machinery

The new findings build on prior research published by Monje's team in 2015. At that time, the scientists showed that neuroligin-3 fueled the growth of high-grade gliomas. This was surprising because the protein is a part of the normal machinery of neuroplasticity in a healthy brain, and it is a relatively new concept that cancer can hijack an organ's healthy function to drive cancer growth.

In the new study, Monje's team examined mice that were genetically engineered to lack neuroligin-3. These mice have nearly normal brain function. However, when their brains were implanted with any of the forms of human high-grade glioma, the cancer cells could not proliferate. The growth stagnation persisted for several months.

"Lack of neuroligin-3 doesn't kill the cancer cells; the cells that are there remain there, but they do not grow," Monje said. However, 4½ months after implantation, tumors in some mice circumvented their dependency on neuroligin-3 and began to grow again, she added.

Effect specific to high-grade gliomas

The researchers also tried implanting the brains of mice lacking neuroligin-3 with human breast cancer cells. Lack of neuroligin-3 did not affect breast cancer growth, showing that the effect is specific to high-grade gliomas.

The growth-stagnation effects, conserved across different classes of high-grade glioma, were unexpectedly strong. To find out why, the researchers conducted follow-up experiments that examined the cell signals involved in neuroligin-3's role in the division of glioma cells, which demonstrated that neuroligin-3 activates multiple cancer-promoting signaling pathways and also increases the expression of genes involved in cell proliferation, promotion of malignancy, function of potassium channels and synapse function. The researchers now believe that neuroligin-3 is more than just a gatekeeper of glioma cell division, though further research is needed to clarify its exact role, Monje said.

The team also explored whether blocking neuroligin-3 has therapeutic potential for treating gliomas. Using mice with normal neuroligin-3 brain signaling and human high-grade gliomas, the researchers tested whether two inhibitors of neuroligin-3 secretion could stop the cancers' growth. One of the inhibitors has never been tested in humans, but the other has already reached phase-2 clinical trials as a potential chemotherapy for other forms of cancer outside the brain.

> "We will have to attack these tumors from many different angles to cure them."

Both inhibitors significantly reduced glioma growth during a short-term trial, suggesting that the strategy of inhibiting neuroligin-3 secretion may help human patients.

'Clear path forward for therapy'

"We have a really clear path forward for therapy; we are in the process of working with the company that owns the clinically characterized compound in an effort to bring it to a clinical trial for brain tumor patients," Monje said. Inhibition of neuroligin-3 will not represent a cure for high-grade gliomas, she cautioned, since it does not kill the cancer cells. Ultimately, she hopes to combine it with other treatment strategies against the tumors.

"We will have to attack these tumors from many different angles to cure them," Monje said. But given how devastating the tumors are, the possibility of using neuroligin-3 inhibition to slow tumor progression is a hopeful development, she added. "Any measurable extension of life and improvement of quality of life is a real win for these patients."

The team's 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 co-authors are undergraduate Lydia Tam; life science research associate Pamelyn Woo; and graduate students James Lennon, Surya Nagaraja and Shawn Gillespie. Monje is a member of Stanford's Child Health Research Institute, the Stanford Institute for Regenerative Medicine and Stem Cell Biology, Bio-X, the Stanford Cancer Institute and the Stanford Neurosciences Institute.

Scientists from Dana Farber Cancer Institute, Harvard Medical School and the National Center for Advancing Translational Sciences also contributed to the study.

The research was funded by the V Foundation; the Liwei Wang Research Fund; the National Institutes of Health; the Department of Defense; the McKenna Claire Foundation; Alex's Lemonade Stand Foundation; The Cure Starts Now Foundation; the DIPG Collaborative; the Lyla Nsouli Foundation; Unravel Pediatric Cancer; the California Institute for Regenerative Medicine; the Childhood Brain Tumor Foundation; the Matthew Larson Foundation; the Joey Fabus Childhood Cancer Foundation; the Wayland Villars DIPG Foundation; the Connor Johnson, Zoey Ganesh and Declan Gloster memorial funds; the N8 Foundation; the Virginia and D.K. Ludwig Fund for Cancer Research; the Stanford Child Health Research Institute; the Breast Cancer Research Foundation; the National Center for Advancing Translational Sciences; and the National Cancer Institute.

Stanford's Department of Neurology and Neurological Sciences also supported the work. ISM

Beth Darnall receives funding to test pain management strategies

Beth Darnall, PhD, clinical associate professor of anesthesiology, perioperative and pain medicine, has received an $8.8 million research award to study how to best help patients with chronic pain reduce opioids.

The study will seek to determine whether cognitive behavioral therapy or pain self-management classes are effective at alleviating pain and reducing opioid use among people with chronic pain.

Darnall, a pain psychologist and researcher, said people with chronic pain are often fearful about reducing opioid use.

"Alternatives are needed to reduce opioid risks *and* to provide pain relief to patients," she said, adding that her study aims to reduce opioid use compassionately while testing the effectiveness of behavioral treatment for pain. "We seek to provide physicians and patients with the evidence and tools they need to treat chronic pain with less opioids."

Beth Darnell

Study participants will begin a patient-centered program to taper their opioid use and will also be assigned to one of three groups: one will receive cognitive behavioral therapy, another will learn pain self-management techniques and the third will receive no behavioral treatment.

Darnall's proposal was among 11 projects that received funding Sept. 12 from the Patient-Centered Outcomes Research Institute. In all, the institute gave $97.9 million for studies comparing different approaches to improving care for a range of health conditions.

The institute is an independent, nonprofit organization that funds research aimed at providing patients and their caregivers with the evidence-based information needed to make better-informed health care decisions. ISM

OF NOTE

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

POSSU HUANG, PhD, was appointed assistant professor of bioengineering, effective Oct. 1, 2016. His research interests include computational and experimental protein engineering, with a focus on developing custom protein structures to address biomedical problems.

DANIEL JAROSZ, PhD, assistant professor of chemical and systems biology and of developmental biology, was named a 2017 Vallee Scholar by the Bert L. and N. Kuggie Vallee Foundation. The award honors outstanding early career scientists who are working to understand basic biological processes. It provides $250,000 over five years. His research examines the effects of protein folding and misfolding on disease and regular development and how frequently mutating cells, such as cancer cells, survive and thrive.

HAROLD PIMENTEL, PhD, a postdoctoral scholar, has been named a Hanna H. Gray fellow by the Howard Hughes Medical Institute. The program, which is intended to support young researchers as they transition from postdoctoral positions to principal investigators, provides up to $1.4 million over eight years, as well as mentoring. He develops computational and statistical methods to understand genomic data.

MANU PRAKASH, PhD, assistant professor of bioengineering, was awarded the 2017 INDEX: Award in the play and learning category for developing the Paperfuge, a low-cost, hand-powered centrifuge. The prize includes 100,000 euros (about $119,000). He received the honor Sept. 1 in Denmark. His focus is on developing low-cost scientific tools, especially ones with clinical applications that could be used in low-resource regions.

BALI PULENDRAN, PhD, was appointed professor of pathology and of microbiology and immunology, effective June 15. His research interests focus on understanding how the immune system senses microbes and viruses and then programming immune responses against them to design vaccines.

JEANNE SHEN, MD, was appointed assistant professor of pathology, effective July 1. She specializes in gastrointestinal and pancreatobiliary pathology, with research interests in gastrointestinal and pancreatic neoplasia, inflammatory bowel disease, and the application of emerging technologies, such as digital image analysis and machine learning, to pathology.

SARA SINGER, PhD, was appointed professor of medicine, effective July 1. Her research examines challenges in health care delivery, including patient safety, the integration of fragmented services and the adoption of innovative practices. She also develops survey tools to measure patient and provider perspectives and interventions to improve teamwork and organizational culture.

JEFFREY TEUTEBERG, MD, was appointed associate professor of medicine, effective July 1. He is the section chief of heart failure, cardiac transplantation and mechanical circulatory support. His research interests include new approaches to immunosuppression and the clinical outcomes of patients who have undergone surgery for a heart transplant or received mechanical heart support.

SHERRY WREN, MD, professor of surgery and director of global surgery at the Center for Innovation in Global Health, has received an American College of Surgeons/Pfizer Surgical Volunteerism Award. The honor recognizes surgeons who are committed to giving back to society by making significant contributions to surgical care. Wren was recognized for her work developing a Stanford course to educate physicians in humanitarian surgery, her commitment to educational and research collaborations in Africa and for her work with Doctors Without Borders in conflict zones in Africa. ISM

Possu Huang

Daniel Jarosz

Harold Pimentel

Manu Prakash

Jeanne Shen

Sara Singer

Jeffrey Teuteberg

Sherry Wren

Program

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he said. "You shouldn't have to rely on luck."

At the end of the evening, students peppered the university president with questions and spoke a bit about how this one-year program helped them. One of the mentees, Rich Trimble, now a second-year medical student, got up to the podium to thank his mentor Robert Harrington, MD, professor and chair of medicine, for his mentorship throughout the year.

"It was really hard getting through the first year of medical school," Trimble said. "It feels really good to be supported."

For Amorin, this past year's mentorship will help him navigate his future career, he said.

"I'm interested in neurosurgery," said Amorin, who after high school found academic success at community college. As a medical student, he faces a whole new range of questions about his future, and his mentor — Natalia Gomez-Ospina, MD, PhD, an instructor in pediatrics and medical genetics, who was born and raised in Columbia — has been there for him, he said.

"She's helped advise me on things like whether it's feasible to do a PhD on top of my MD."

"She's helped advise me on things like whether it's feasible to do a PhD on top of my MD," he said. "She's been through it. She knows what it's like."

The program, which is sponsored by the Office of Medical Student Affairs, the Office of Graduate Education and the Stanford Medicine Alumni Association, begins a new academic year in October, pairing new first-generation students with mentors. ISM

Pain

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absences for hospital stays, fatigue and stress, as well as memory issues associated with his medications, took a toll on his schoolwork. That is when Kane learned about the family, referred to her by Suresh's care team, and stepped in to offer support.

A big part of HEAL's function is educating students, parents and schools about the unique cognitive, social and emotional needs of medically fragile children in order to obtain appropriate school services. In Suresh's case, his mother, Pannaga Parthasarathy, had exhausted her efforts as his advocate. "At a certain point, I didn't know what else to ask for to help him in school," she said.

Kane worked with the family and the school for three years, with much time dedicated to rigorously advocating the case for Suresh to receive educational accommodations based on his medical conditions.

When he received his acceptance to UC-Davis, the joy and accomplishment was a celebrated victory for everyone in his life as well as a sense of relief for his family, knowing that he wouldn't be too far away.

"I feel so honored to work with him," said Kane. "He fought so hard to get to where he is."

According to Berquist, Suresh and his care team are finding success managing Suresh's conditions with immunosuppressive treatment, which requires IV infusions monthly. Suresh will be back to Stanford once a month to receive his infusions. His mom will be happy to see him, and said she's getting advice from other moms with kids in college to "not be obsessive and show up at school all the time."

As for Suresh, he said, "I'm most looking forward to being a college student, feeling like a normal kid, not feeling different, not being a patient — getting the chance to live my life." ISM