INSIDE STANFORD MEDICINE

Volume 11, No. 1 ■ January 14, 2019 ■ Published by the Office of Communication & Public Affairs

Programs for patients at Lucile Packard Children's Hospital Stanford are broadast from the hospital's new studio.

Page 5

Facing adversity, Sibley finds path to success

By Julie Greicius

STEVE FISCH

Eric Sibley, professor of pediatric gastroenterology, arrived at Stanford in 1993 and worked in the lab of Gary Gray as a postdoctoral scholar.

At first, the symptoms were so subtle he hardly noticed them.

Sometimes his foot would catch on the ground when he walked. "I would stumble a little bit," said Eric Sibley, MD, PhD, professor of pediatric gastroenterology at the School of Medicine. "Gradually it became more pronounced, until it was an obvious limp."

A young physician-scientist, Sibley's focus was on the patients he cared for and the scientific discoveries he was working to achieve. Since his arrival at Stanford in 1993 as a postdoctoral scholar, he'd been investigating why the gene involved in making lactase, an enzyme responsible for lactose digestion, gets turned off in most mammals after they're weaned. His goal was to understand the gene regulation behind this developmental phenomenon and apply what could be learned to regulating other genes in the gastrointestinal tract.

He cared for patients in the pediatric gastroenterology clinic at Lucile Packard Children's Hospital Stanford. "The dominant theme of Eric's practice is caring about the people who need it most," said Dorsey Bass, MD, associate professor of pediatric gastroenterology, who shared a Friday afternoon clinic with Sibley for two decades. Some of Sibley's patients, Bass said, were "very financially distressed and with multiple disabilities, kids with cerebral palsy and lots of complicated, difficult issues. Eric's loyalty to them and their loyalty to him just always, well — it makes you a little proud to be a human."

Sibley couldn't yet know how his own medical diagnosis would affect his life and career path. While his physical limitations would not change his aspirations, they increasingly opened him to his strengths as an academic mentor and role model of resilience.

A persistent shoulder injury

When he wasn't working, Sibley enjoyed time with his wife, Carol Somersille, MD, an obstetrician-gynecologist, and their two children, Carl Somersille Sibley and Lauren Somersille Sibley, whom he credits with providing invaluable support. Sibley coached his son's and daughter's basketball teams. He played golf and softball, too. But after a round of golf in 1999, Sibley became aware of a shoulder injury that wouldn't go away.

An MRI of his shoulder didn't show much, but looking toward Sibley's spine, the doctor noticed demyelinating lesions — evidence that the protective covering, called myelin, around his nerve fibers was damaged. It wasn't enough for a diagnosis of multiple sclerosis — a brain and spinal cord disease in which the immune system attacks the myelin wrapping of nerve cells — but it was suspicious.

Sibley's official diagnosis didn't come until many years later, but when it did it was severe: primary progressive multiple sclerosis, the most aggressive form of the disease.

A career interrupted

For Sibley, the adjustment to becoming a patient — a doctor-patient using a cane, then forearm crutches and eventually a wheelchair — was challenging. "Until I developed MS, I was thinking, 'OK, I'm going to be able to do everything,'" he said. "It was a big psychological evolution to be able to accept that, yeah, there are going to be limitations on what I can do and how people are going to perceive me. The first real hurdle was using a crutch at all."

See SIBLEY, page 6

Strength in weakness: 'Fragile' DNA regions key to vertebrate evolution, according to scientists

By Krista Conger

Regions of DNA susceptible to deletion during replication may have allowed vertebrates to successfully adapt to rapidly changing environmental conditions during evolution, according to a study by researchers at the School of Medicine.

The research suggests that some critical evolutionary changes are likely to have occurred in leaps and bounds through the abrupt loss of stretches of DNA, rather than through the slow accumulation and additive effects of many small mutations.

KATHY XIE

A painting of threespine sticklebacks adorns the office of David Kingsley. He studies evolutionary changes in the tiny fish.

The researchers, who studied a tiny fish called the threespine stickleback, found that such "fragile" DNA regions create genetic hot spots that mutate much more rapidly, and dramatically, than neighboring sequences. The resulting changes can help an organism vault far ahead of its peers in the evolutionary arms race.

Although similar findings have been described in bacteria, this is one of the first studies to show that the same process has occurred in vertebrates to create dramatic changes in body structure. It also addresses a long-standing mystery in evolutionary biology.

"There is a lot of evidence that the same genes across different populations or species are often responsible for similar evolutionary changes," said David Kingsley, PhD, professor of developmental biology. "What hasn't been clear is why this is happening. This study describes at a biochemical level, down to the atoms and sequences in DNA, how a particular type of mutation can arise repeatedly, which then contributes to a complex skeletal trait evolving over and over again in wild fish species. It's a great example of how DNA fragility can sometimes contribute to favorable traits rather than diseases in natural populations, and it may give us important insights into the process of human evolution."

Kingsley, a Howard Hughes Medical Institute investigator, is the senior author of the study, which was published Jan. 4 in *Science*. Graduate

See FISH, page 5

Physical therapy can reduce risk, amount of long-term opioid use, new study finds

By Amy Jeter Hansen

Patients who underwent physical therapy soon after being diagnosed with pain in the shoulder, neck, low back or knee were approximately 7 to 16 percent less likely to use opioids in the subsequent months, according

See OPIOIDS, page 7

TB STUDIO/SHUTTERSTOCK.COM

Physical therapy within three months of a musculoskeletal pain diagnosis reduced patients' risk of long-term opioid use by about 10 percent, Stanford and Duke scientists found.

Developing radiation therapy with a brief exposure time

By Manuel Gnida

New accelerator-based technology being developed by the Department of Energy's SLAC National Accelerator Laboratory and Stanford University aims to reduce the side effects of cancer radiation therapy by shrinking its duration from minutes to under a second.

Researchers at SLAC and Stanford received funding to develop two possible treatments for tumors — one using X-rays, the other using protons. The idea behind both is to blast cancer cells so quickly that organs and other tissues don't have time to move during the exposure, much like taking a single freeze frame from a video. This reduces the chance that radiation will hit and damage healthy tissue around tumors, making radiation therapy more precise.

"Delivering the radiation dose of an entire therapy session with a single flash lasting less than a second would be the ultimate way of managing the constant motion of organs and tissues, and a major advance compared with methods we're using today," said Billy Loo, MD, PhD, an associate professor of radiation oncology.

Sami Tantawi, PhD, a professor of particle physics and astrophysics and the chief scientist for the RF Accelerator Research Division in SLAC's Technology Innovation Directorate, works with Loo on both projects. "In order to deliver high-intensity radiation efficiently enough, we need accelerator structures that are hundreds of times more powerful than today's technology," Tantawi said. "The funding we received will help us build these structures."

Blasting cancer with X-rays

A project called PHASER aims to develop a flash delivery system for X-rays.

In today's medical devices, electrons fly through a tube-like accelerator structure that's about a meter long, gaining energy from a radiofrequency field that travels through the tube at the same time and in the same direction. The energy of the electrons then gets converted into X-rays. Over the past few years, the PHASER team has developed and tested accelerator prototypes with special shapes and new ways of feeding radiofrequency fields into the tube. These components are already performing as predicted by simulations and could pave the way for accelerator designs that support more power in a compact size.

"Next, we'll build the accelerator structure and test the risks of the technology, which, in three to five years, could lead to a first actual device that can eventually be used in clinical trials," Tantawi said.

The Department of Radiation Oncology will provide about $1 million over the next year for these efforts and support a campaign to raise more research funding. In collaboration with the School of Medicine, the department also has established the Radiation Science Center, which focuses on precision radiation treatment. Its PHASER division, co-led by Loo and Tantawi, aims to turn the PHASER concept into a functional device.

Making proton therapy agile

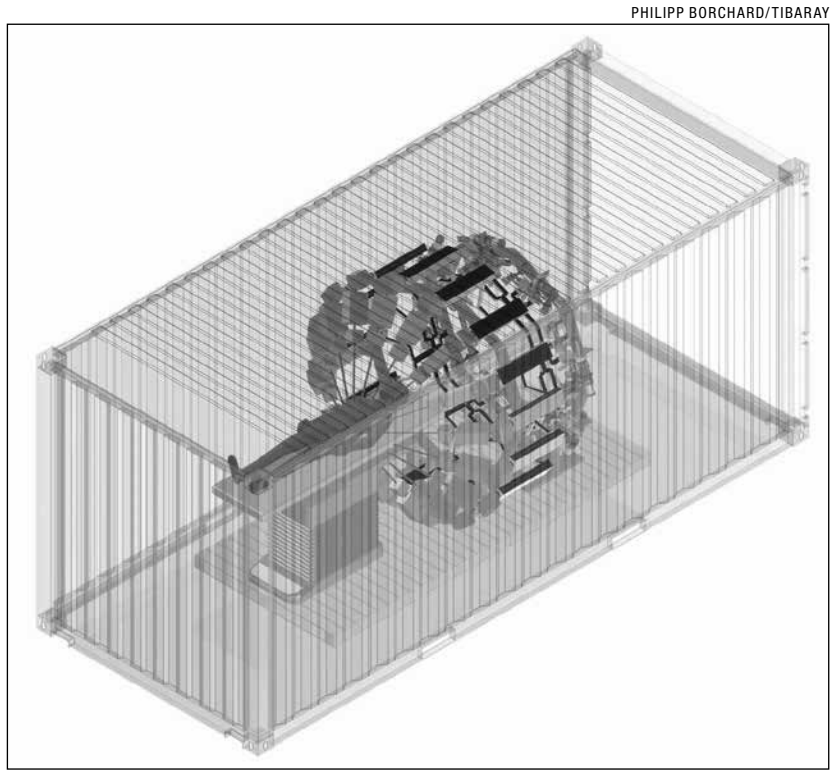
In principle, protons are less harmful to healthy tissue than X-rays because they deposit their tumor-killing energy in a more confined volume inside the body. However, proton therapy requires large facilities to accelerate protons and adjust their energy. It also uses magnets weighing hundreds of tons that slowly move around a patient's body to guide the beam to the target.

"We want to come up with innovative ways to manipulate the proton beam that will make future devices simpler, more compact and much faster," said Emilio Nanni, PhD, a staff scientist at SLAC who leads this project with Tantawi and Loo.

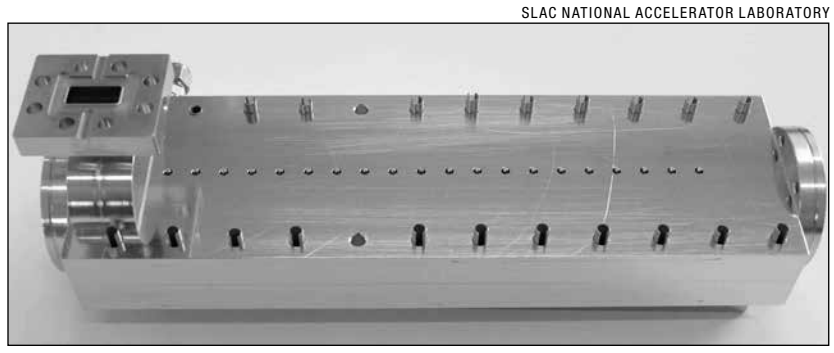
That goal could soon be within reach, thanks to a recent $1.7 million grant from the DOE Office of Science Accelerator Stewardship program to develop the technology over the next three years.

"We can now move forward with designing, fabricating and testing an accelerator structure similar to the one in the PHASER project that will be capable of steering the proton beam, tuning its energy and delivering high radiation doses practically instantaneously," Nanni said.

PHILIPP BORCHARD/TIBARAY



SLAC NATIONAL ACCELERATOR LABORATORY



(Top) The proposed PHASER design is compact enough to fit into standard cargo containers. (Bottom) A prototype accelerator component for the PHASER project.

Quick, effective and accessible

In addition to making cancer therapy more precise, flash delivery of radiation also appears to have other benefits.

"We've seen in mice that healthy cells suffer less damage when we apply the radiation dose very quickly, and yet the tumor-killing effect is equal to or even a little bit better than that of a conventional longer exposure," Loo said. "If the result holds for humans, it would be a whole new paradigm for the field of radiation therapy."

Another key objective of the projects is to make radiation therapy more accessible for patients worldwide.

Today, millions of patients around the world receive only palliative care because they don't have access to cancer therapy, Loo said. "We hope that our work will contribute to making the best possible treatment available to more patients in more places."

That's why the team is focusing on designing systems that are compact, power-efficient, economical, efficient to use in the clinical setting and compatible with existing infrastructure around the world, Tantawi said.

"The first broadly used medical linear accelerator design was invented and built at Stanford in the years leading up to the building of SLAC," he said. "The next generation could be a real game changer — in medicine and in other areas, such as accelerators for X-ray lasers, particle colliders and national security."

Peter Maxim, PhD, a former assistant professor of radiation oncology at Stanford, is a co-inventor of PHASER and made key contributions to both projects. Members of the proton therapy include researchers at Loma Linda University and Varian Medical Systems. **ISM**

Health care democratization underway, according to Health Trends Report

An explosion in data is driving increased democratization in health care, according to the second annual Health Trends Report published Dec.13 by Stanford Medicine.

Building on last year's findings about the emergence and changing role of data in medicine, the latest report takes a deeper look at how using and sharing data will transform research, the practice of medicine and the role patients play in their own health care.

This transformation is being driven by the growing volume of available data across the health care system, as well as new technologies and industry players that are taking medical knowledge from a human scale to a digital scale.

"We are on the cusp of something that's never been possible before — the ability to truly democratize the practice of health care, spreading expertise without friction wherever it's needed," said Lloyd Minor, MD, dean of the School of Medicine. "Whole realms of expertise, previously siloed, are beginning to open up to more people in more places than ever before.

> "We are on the cusp of something that's never been possible before."

"It's clear that we have work to do in terms of making this incredible amount of data easier to access, share and protect," he added. "But I am certain that we are advancing toward a future of care that is more preventive, predictive, personalized and precise."

Findings

The report reflects a comprehensive review and analysis of existing health care research and publicly available data on the current and emerging trends facing the health care sector, combined with insights from Stanford faculty and external health care experts.

The report identifies three main pillars influencing the democratization of health care: intelligent computing, sharing and data security.

Intelligent computing: Artificial intelligence and data analytics are rapidly improving as tools to manufacture insights from health data at scale. This is likely to result in health care that is more precise and efficient, drawing cost out of the system and eliminating bottlenecks for providers and patients alike. With the size of the AI health market expected to reach $6.6 billion by 2021, AI's impact on the medical field will have significant near- and long-term effects. However, as the health care industry embraces the potential of AI, it must take certain practical and ethical steps to ensure its safety. Intelligent computing has the potential to make health care more personalized, accessible and efficient, but only if the industry is prepared to take on the challenges that come with it.

Sharing: Information sharing must be improved **See TRENDS, page 3**

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

Stanford Children's Health to increase telehealth appointments

By Samantha Beal

These days it's hard to find someone who doesn't use digital health technology. Most of us go online to make appointments, access our medical records, look at test results and exchange notes with our doctor's office. Many of us take advantage of remote virtual appointments and use devices to track health data that can give providers a broader picture of our well-being.

Digital health technology is also helping Stanford Children's Health offer patients and their families better access to Stanford Medicine pediatric experts. This year, Stanford Children's plans to more than double its number of telehealth appointments — from 1,100 visits in 2018 to 2,500 visits in 2019.

Currently, telehealth visits are offered to patients for follow-up appointments. Some of those are clinic-to-clinic visits, in which a nurse practitioner at a primary care office connects with a physician at a specialty clinic.

During a clinic-to-clinic visit, a nurse practitioner at the remote clinic examines the child while a high-resolution camera and microphone let the physician at the specialty clinic see and hear exactly what the nurse practitioner does.

Vandna Mittal, director of digital health services at Stanford Children's Health, said these clinic-to-clinic telehealth visits are used for an array of appointments, from diagnosing eye problems in premature infants to performing video electroencephalograms for neurology. Because the Stanford Children's Health network spans from Santa Rosa to Salinas, these virtual visits help families fit appointments into their schedules.

"Through virtual visits, we are not only saving families time traveling to appointments and taking their kids out of school and work, we are also maximizing our providers' ability to see more patients, fill in last-minute cancellations and accommodate urgent requests," Mittal said.

> "Digital health allows more flexibility and greater access to the best care available."

Enabling more realistic evaluation

Patients also benefit from clinic-to-home telehealth visits. Through the Stanford Children's Health MyChart patient portal, patients and families can connect with their physicians remotely using their own devices, such as phones and tablets. Mittal said such virtual visits are popular among teen behavioral-health patients who go away to college but want to maintain a close relationship with their mental health provider at Stanford. Providers at the developmental-behavioral clinic are using these visits to observe patients in their natural play environments, at home or even on the playground, enabling a more realistic evaluation of the child's condition.

In addition, Stanford Children's Health offers clinic-to-school visits, in which physicians can connect remotely with a patient in a school nurse's office. For instance, a physician caring for a child with Type 1 diabetes can communicate directly with the school nurse and the patient's parent through a telehealth visit at the nurse's office, minimizing the need for the parents and the child to travel to the doctor's office and enabling the doctor and the school nurse to interact. According to Mittal, this approach is working well among patients with diabetes who may live far away from the hospital, but require ongoing support and blood glucose monitoring.

Telehealth is also being used within Packard Children's Hospital. From inpatient units, on-call doctors are evaluating patients in the emergency department via telehealth before they are admitted; in some cases, specialists are able to advise ED care teams on the most appropriate transfer methods for patients. This approach cuts down on provider walking time and limits the time families spend waiting for care consultations.

"Although virtual telehealth visits are not a blanket solution for everyone or every visit, they are instrumental in helping patients and families who require more care or live away from their specialists, without sacrificing that vital connection," Mittal said. "Thanks to advances in medicine and science, we are able to care for more children with chronic or serious conditions than ever before, and digital health allows more flexibility and greater access to the best care available."

Digital second opinions

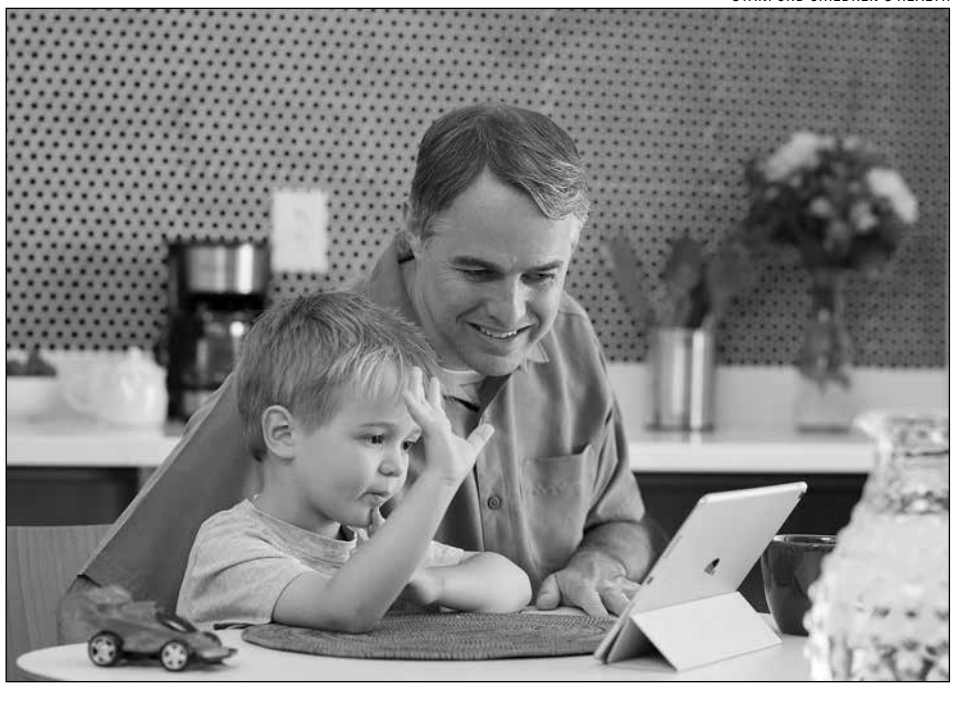
In November, Stanford Children's Health launched a new service in conjunction with Stanford Health Care that offers digital second opinion consultations from Stanford physicians. Patients don't have to visit the hospitals or clinics for this service. *(See story, this page).*

Mittal noted that Stanford Children's Health's multipronged digital health approach — including telehealth, remote care monitoring and patient portal access — will continue to empower families and patients to manage their health care and enable providers to make better-informed care decisions. **ISM**

STANFORD CHILDREN'S HEALTH

Families can connect with Stanford Children's Health specialists from their pediatricians' office, minimizing the need to travel long distances and take time from work and school.

STANFORD CHILDREN'S HEALTH



Through the Stanford Children's Health MyChart patient portal, patients and families can visit with their physicians remotely using their own devices, such as mobile phones and tablet computers.

Trends

continued from page 2

at a foundational level to allow data to flow freely between various participants in the system, including health care providers, patients, technology providers and insurers. While the health care industry still faces challenges with data sharing, there are exciting advances being made through collaborations between traditional health care players and new market entrants.

Data security: A more open data environment underscores the importance of the security, privacy and safety of patient information. Ensuring patient data is protected will continue to be a priority as the medical industry realizes the need to become more intentional about information-security practices and preparedness. Striking a balance between encouraging innovation and safeguarding this highly personal information will require cooperation between the medical and technology industries, as well as with government entities that are becoming more involved in the regulation of digital health.

An online version of the report, including the executive summary, can be found at med.stanford.edu/healthtrends. **ISM**

Online second opinion program launched at Stanford Medicine

Stanford Health Care and Stanford Children's Health have launched a new online program that provides patients with a second opinion about their diagnosis or treatment plan.

A Stanford Medicine specialist develops the second opinion based on a patient's summary of his or her conditions and initial diagnosis, as well as all relevant medical records. The medical records are collected on behalf of the patient, if the records are in the United States.

The specialist sends a written second opinion to the patient and his or her doctor, usually within two weeks. The cost for the second opinion service is $700 and is available to patients in almost every location. (Most health plans do not cover online second opinions.)

To get access to the service, adult patients can create an account on the Stanford Medicine Online Second Opinion website at https://stanfordhealthcare.org/second-opinion/overview.html.

For patients 17 or younger, parents may create an account at the Stanford Children's Health Online Second Opinion website at http://secondopinion.stanfordchildrens.org.

Online second opinions for children are available for a limited number of specialties and conditions, including otolaryngology, orthopedics and epilepsy. For parents of pediatric patients who are being considered for neurosurgery, heart transplantation, heart failure treatments or cardiothoracic surgery, a medical record review service provides evaluation of eligibility for surgery. This service is complimentary to patients who already have a diagnosis in the participating specialty, may require surgery and are considering options. **ISM**

Scientists design battery-free, biodegradable blood flow sensor

By Taylor Kubota

A new device developed by Stanford University researchers could make it easier for doctors to monitor the success of blood vessel surgery.

The sensor, detailed in a paper published Jan. 8 in *Nature Biomedical Engineering*, monitors the flow of blood through an artery. It is battery-free, wireless and biodegradable, so it doesn't need to be removed. It can warn a patient's doctor if there is a blockage.

"Measurement of blood flow is critical in many medical specialties, so a wireless biodegradable sensor could impact multiple fields, including vascular, transplant, reconstructive and cardiac surgery," said Paige Fox, MD, PhD, assistant professor of surgery and a senior author of the paper. "As we attempt to care for patients throughout the Bay Area, Central Valley, California and beyond, this is a technology that will allow us to extend our care without requiring face-to-face visits or tests."

Monitoring the success of surgery on blood vessels is challenging, as the first sign of trouble often comes too late. By that time, the patient often needs additional surgery that carries risks similar to the original procedure. The new sensor could let doctors keep tabs on a healing vessel from afar, creating opportunities for earlier interventions.

Flow or no

The sensor wraps snugly around the healing vessel, where blood pulsing past pushes on the sensor's inner surface. As the shape of that surface changes, it alters the sensor's capacity to store electric charge, which doctors can detect remotely from a device located near the skin but outside the body. That device solicits a reading by pinging the antenna of the sensor, similar to an ID card scanner. In the future, this device could come in the form of a stick-on patch or be integrated into other technology, like a wearable device or smartphone.

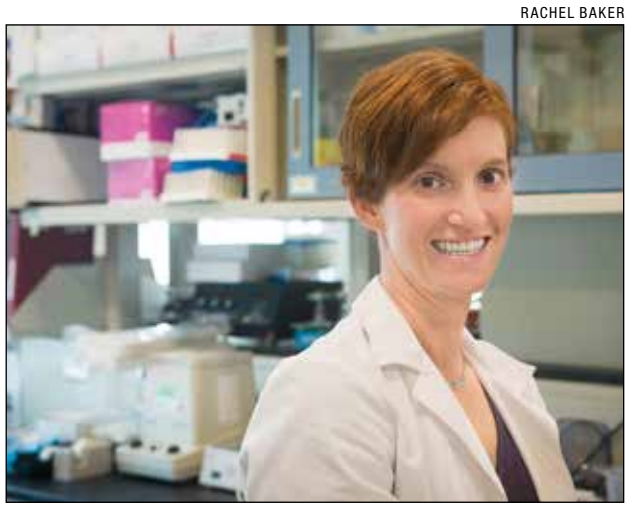
The researchers first tested the sensor in an artificial setting where they pumped air through an artery-sized tube to mimic pulsing blood flow. Surgeon Yukitoshi Kaizawa, MD, PhD, a former postdoctoral scholar at Stanford and co-author of the paper, also implanted the sensor around an artery in a rat. Even at such a small scale, the sensor successfully reported blood flow to the wireless reader. At this point, the researchers were only interested in detecting complete blockages, but they did see indications that future versions of the sensor could identify finer fluctuations of blood flow.

The sensor is a wireless version of technology that chemical engineer Zhenan Bao has been developing to give prostheses a delicate sense of touch.

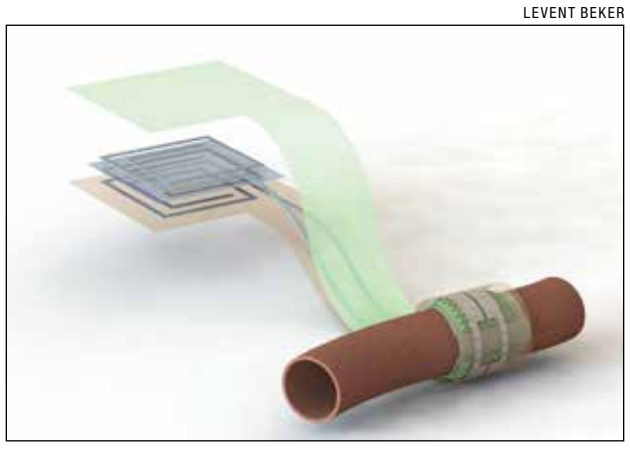
"This one has a history," said Bao, PhD, the K. K. Lee Professor and the paper's other senior author. "We were always interested in how we can utilize these kinds of sensors in medical applications, but it took a while to find the right fit."

The researchers had to modify their existing sensor's materials to make it sensitive to pulsing blood but rigid enough to hold its shape. They also had to move the antenna to a location where it would be secure, not affected by the pulsation, and redesign the capacitor so it could be placed around an artery.

RACHEL BAKER



LEVENT BEKER



(Top) Paige Fox and her collaborators say the blood flow sensor they've developed could let doctors keep tabs on a healing blood vessel from afar. (Below) A rendering of the biodegradable pressure sensor wrapped around a blood vessel with the antenna off to the side (layers are separated to show details of the antenna's structure).

"It was a very exacting project and required many rounds of experiments and redesign," said postdoctoral scholar Levent Beker, PhD, a lead author of the paper. "I've always been interested in medical and implant applications, and this could open up a lot of opportunities for monitoring or telemedicine for many surgical operations."

Making connections

The idea of an artery sensor began to take shape when Clementine Boutry, then a postdoctoral scholar in the Bao lab, reached out to Anaïs Legrand, then a postdoctoral scholar in the Fox lab, and connected those groups — along with the lab of James Chang, MD, the Johnson and Johnson Professor in Surgery. (Boutry is the paper's other lead author.)

Once they set their sights on the biodegradable blood flow monitor, the collaboration won a 2017 Postdocs at the Interface seed grant from Stanford ChEM-H, which supports postdoctoral research collaborations exploring potentially transformative new ideas.

"We both value our postdoctoral researchers but did not anticipate the true value this meeting would have for a long-term productive partnership," Fox said.

The researchers are now finding the best way to affix the sensors to the vessels and refining their sensitivity. They are also looking forward to what other ideas will come as interest grows in this interdisciplinary area.

"Using sensors to allow a patient to discover problems early on is becoming a trend for precision health," Bao said. "It will require people from engineering, from medical school and data people to really work together, and the problems they can address are very exciting."

Bao is a member of Stanford Bio-X, a senior fellow at the Precourt Institute for Energy, a fellow at Stanford ChEM-H, an affiliate of the Stanford Woods Institute for the Environment and a member of the Wu Tsai Neurosciences Institute at Stanford. Chang is a member of Stanford Bio-X. Fox is a fellow at Stanford ChEM-H.

Other Stanford co-authors are Christopher Vassos, Helen Tran, Allison Hinckley, Raphael Pfattner, Simiao Niu, Junheng Li, Jean Claverie, Zhen Wang.

This work was funded by the Swiss National Science Foundation, the European Commission, Stanford ChEM-H and the National Science Foundation. ISM

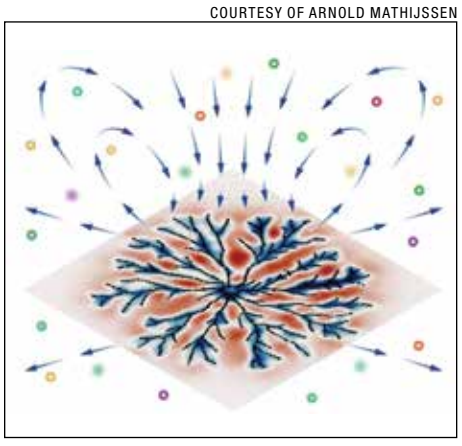
Researchers decipher flows that help bacteria feed, organize biofilms

By Taylor Kubota

Under threat of being scrubbed away with disinfectant, individual bacteria can improve their odds of survival by joining together to form colonies, called biofilms. What Arnold Mathijssen, PhD, wanted to understand was how stationary biofilms find food once they've devoured nearby nutrients.

Leading an international team of researchers in creating simulations of how fluids move, Mathijssen, a postdoctoral scholar in bioengineering at Stanford, found that individual bacteria and biofilms can generate currents strong enough to draw in distant nutrients.

COURTESY OF ARNOLD MATHIJSSEN



This depiction of a bacterial colony, arranged in a branching pattern, shows how the bacteria can create a swirling current that pulls in nutrients, shown here as colored dots.

In their work, published Dec. 11 in *Physical Review Letters*, the researchers were able to find predictable patterns of how fluids move based on the general shapes of biofilms, insights that could find applications in many fields.

"There is a very strong universality in the physical properties of micro-hydrodynamics," said Mathijssen, who works in the lab of Manu Prakash, PhD, associate professor of bioengineering. "We've talked about bacteria, but we could replace the word 'organism' with 'microrobot' and the physics would be exactly the same."

Starting simple

When bacteria move, they disturb the liquids that surround them. The researchers explored the strength of that disturbance in a single bacterium that moves in a way similar to many pathogenic species, including those that cause gastritis and cholera. They found that as this bacterium swims forward, it creates a tiny but stable current in the surrounding liquid with fluid moving toward its center and away from the head and tail.

Then, they calculated the flows produced by a colony of randomly arranged bacteria and were surprised to see that it created a strong, consistent tide capable of pulling in nutrients. This occurred regardless of the orientation of each bacterium, so long as the colony was thicker in some areas than others, which causes fluid to move from high points to low points. Simulations of more orderly bacteria resulted in even stronger circulation.

Within organized biofilms, the researchers found two common patterns of movement: vortexes and asters. In a vortex pattern, the bacteria move in concentric circles and produce a flow that brings nutrients down to the biofilm's center and then pushes the fluid out the sides. In an aster pattern, the bacteria move toward a central point, creating a flow that moves from the edge of the biofilm until it rises back up, over the center.

"The powerful thing about this is you can add these patterns up," Mathijssen said. "Rather than having to know the position and orientation of every single bacterium, you only need to know the basic patterns that make up the colony, and then it's very easy to derive the overall transport flow."

Seeing what's hidden

The researchers were able to combine vortex and aster patterns within a single biofilm to determine how the bacteria would push, pull and whirl the fluids around them. As a final test, the researchers took calculations representing the complex, realistic motion of bacteria swarming — as they might on the surface of a table — and predicted the strength of that swarm's transport flow. The result were large vortices that spanned distances beyond the boundaries of the biofilm, suitable for keeping the colony fed.

This work started with simple curiosity about the invisible flow of fluids around bacteria. But what the researchers discovered could be quite practical, guiding ways of cutting off an infectious biofilm's source of food, for example. What's more, because it only takes into account a bacterium's shapes and movement, the research also could apply to inanimate objects like synthetic drug delivery mechanisms or micro-robots.

"This started off as a relatively fundamental problem but turned out to be more relevant for biomedical applications than we would have predicted," Mathijssen said. "That's what excites me: We just stumbled upon an idea that, by curiosity, drove us in a very different direction than where we started, and what we found has a lot of potential."

Researchers affiliated with Mayor University in Chile, the University of Chile, Pennsylvania State University and the University of Dusseldorf also contributed to the work.

The study was funded by the Human Frontier Science Program, the Ministry of Economy, Development and Tourism in Chile and the German Research Foundation.

Stanford's Department of Bioengineering, which is jointly managed by the School of Medicine and School of Engineering, also supported the research. ISM

Packard Children's broadcast studio brings fun and a way to connect

By Samantha Beal

The countdown begins: 3, 2 and 1. "Hey guys, it's Mat and Brianna, and we are live in Sophie's Place studio right now."

Brianna Chambers and Mat Vido, studio coordinators in the Sophie's Place Broadcast Studio in Lucile Packard Children's Hospital Stanford, are streaming through the hospital's closed-circuit television channel, Get Well TV. Their show, Radio Talk Show (despite the name, patients can watch as well as listen), was the studio's first live broadcast after months of preparation and planning. It launched in October.

The bubbly duo sound much like the personalities on radio stations and podcasts. They chat about how they spent their weekends, how much they love *The Incredibles 2*, national cupcake day, the perfect pizza toppings and other important topics — like the difference between French dips and Fun Dip. The half-hour show, which airs one to two times weekly, is punctuated with music and calls from patients, listening or watching from their rooms, who answer questions posed by the hosts, such as whether it's appropriate to start playing holiday music before Thanksgiving.

'Social and creative outlet'

For patients like 10-year-old Morgan Passalacqua, the studio can be a fun distraction.

"The shows and programs really lifted her spirits," said her mother, Stacey Passalacqua. "She was going through some tough procedures, and it always put a smile on her face."

Stacey said that "show time" was a bright spot for her daughter and everyone on the unit, including the nurses and staff.

"Children in the hospital often experience extreme periods of isolation when they are unable to interact with their peers as they would normally at school or in their communities," Chambers said. "Sophie's Place offers this social and creative outlet that allows connection and play through technology."

Sara Devaney, the Sophie's Place studio manager, said such connections are important in giving young patients a sense of community while they are in the hospital. During their stay at Packard Children's, the youngsters can tune in and see kids who are also receiving care for illnesses and injuries.

"We had one little girl share her cancer diagnosis and remove her princess tiara to show the audience her bald head," Vido said. "Other children watched the bravery of the girl, then took the courageous step to participate on air after previously feeling too self-conscious."

Live and recorded shows

In addition to the live talk show, the studio offers daily live and recorded shows, including game shows and "kids' choice" programs, in which youngsters can help select what they will see that day based on the week's shows. Patients can also come into the studio to participate on air or call in from their hospital rooms to interact with the studio team and other patients.

The hospital's child-life studio team is committed to finding ways to connect with all patients, ranging from toddlers to teens, as well as their siblings in ways that are meaningful for each. "We strive to provide opportunities for all ages here in the studio," Vido said. "We have game shows based on *Sesame Street* or Disney trivia that speak to our youngest patients, and we create opportunities that are just for teens, like our radio talk show segments where patients call in to share their thoughts or ideas on a given subject. Teens have also joined as co-hosts for some of our TV segments."

The team notes that even though the studio produces "mass media," the experience of watching or listening to the shows, or participating in them, can be quite personal and fulfilling for patients. They recalled one boy who came to the studio daily before it had officially opened to film his own projects. He had been in the hospital for many months, and the studio was a place where he thrived. He gained new skills like hosting, editing and interviewing. He inspired the team with new ideas for ways to use the space.

STANFORD CHILDREN'S HEALTH

Matt Vido and Brianna Chambers host a live show that patients can watch in person or from their hospital rooms. The show is part of the programming created in Sophie's Place Studio at Packard Children's.

"It is incredibly rewarding to see patients engaged in something, whether it be crafts, singing or just listening to music, and it actually helps them express what they are going through," Chambers said. "It's pretty powerful."

The funding for Sophie's Place was donated by NFL Hall of Fame quarterback Steve Young and his wife, Barb, through their Forever Young Foundation.

To support the studio please contact Lauren Ploch at lauren.ploch@lpfch.org or (650) 736-8280. ISM

Fish

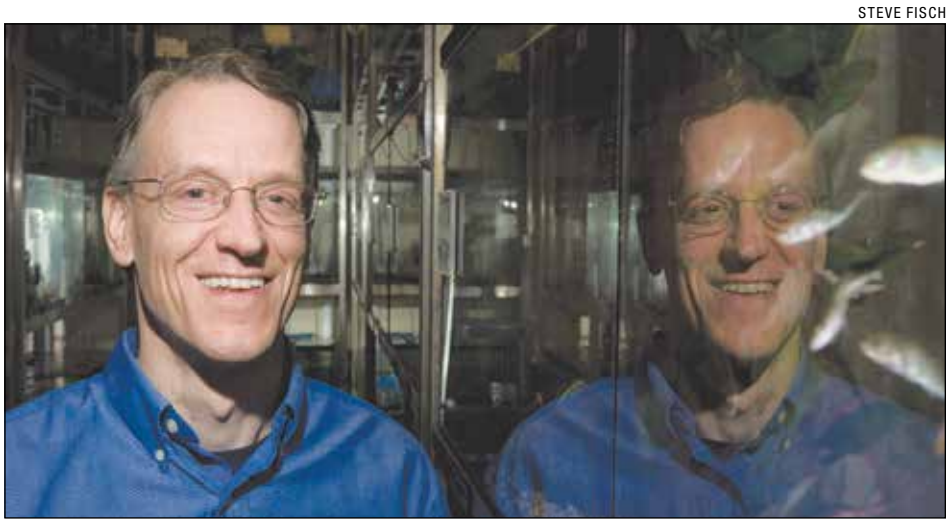
continued from page 1

student Kathleen Xie is the lead author of the work.

Large changes, large effects

Many mutations involve a change in just a single nucleotide, or letter, of DNA. Few of these "point" mutations will confer an evolutionary advantage on their own. Instead, significant change often requires the gradual accumulation of several such mutations. In contrast, sudden, large changes in the genome can have large effects — changing body structure through skeletal modifications or affecting metabolism or brain function, for example. Often, these changes are deleterious, decreasing the chances of an animal's survival. Occasionally, however, the changes are advantageous.

STEVE FISCH



Studying the threespine stickleback, David Kingsley and his colleagues found that DNA regions susceptible to breakage and loss are genetic hot spots for important evolutionary changes.

When the last Ice Age ended, about 10,000 years ago, pockets of migratory ocean threespine sticklebacks colonized newly formed lakes and streams in coastal regions, and then evolved independently in response to their new local environments. As a result, many of these populations show significant differences in body structure. Marine sticklebacks, for example, have a hind fin with a large spine projecting down from their pelvic structure. In contrast, dozens of freshwater populations have lost that hind fin; its absence likely reduces their need for calcium and chances of being nabbed and eaten by hungry insects.

Previous studies in the Kingsley laboratory have identified the loss of a specific DNA regulatory region, called the Pel enhancer, as the repeated cause of the missing hind fins in many populations of the freshwater fish. The Pel enhancer drives the expression of a protein necessary to trigger hind fin development. In this study, Xie used marine stickleback DNA to investigate the Pel region that is missing in its freshwater brethren to learn why that region was particularly susceptible to loss.

Xie found that the DNA sequence of the Pel region is unusual in several ways. Unlike surrounding regions, which exhibit the normal, more-stable helical twist associated with most DNA, the Pel enhancer region that was lost formed an alternate DNA structure predicted to be highly flexible and likely to be unstable during DNA replication. The sequence also contains long strings of repeated pairs of nucleotides, like a kind of genetic stutter. Previous studies in bacteria, mice and humans have indicated that these repeats are often associated with deletions of stretches of DNA.

More frequent chromosome breaks

When Xie tested the stability of the missing Pel region by inserting it into artificial yeast chromosomes, she found that the chromosome broke about 25 to 50 times more frequently than typical DNA sequences. When Xie and her collaborators then tested similar DNA sequences in mammalian cells, they observed that the key dinucleotide repeat sequence often led to the deletion of sections of DNA more than 100 nucleotides long.

The increase in the rate of chromosome breakage observed by Xie, coupled with the likelihood that this damage causes deletions of entire sections of DNA, may have been a key factor in allowing the prominent hind fin skeletal trait to emerge over and over again in many different young stickleback populations. Elevated mutation rates may play a similar role when advantageous traits arise in other organisms, the scientists believe.

"Many vertebrates, including early humans, are dealing with a small population size and relatively long generation times," Kingsley said. "There aren't that many generations available in which to evolve new, potentially advantageous traits. Under these conditions, it may be particularly important for mutations to occur at elevated rates, and to have sweeping effects."

When the researchers investigated known instances of adaptive changes in humans, they found that about half were due to mutations that also arise at elevated rates compared with more typical DNA letter changes.

"What we're learning is that 'arrival of the fittest,' or the relative speed with which a potentially favorable mutation arises, can sometimes be as important as 'survival of the fittest,'" Kingsley said. "The mutation process itself has an important effect on the outcome, and the arrival of the mutation interacts with its effect on the fitness of the organism to bring about major changes in vertebrate evolution."

Other Stanford authors are former graduate student Abbey Thompson, PhD, and graduate student Julia Wucherpfennig. Researchers from the University of Texas-Austin, the University of Victoria, the University of Nottingham, the University of British Columbia and the University of California-Berkeley also contributed to the study.

The research was supported by the National Institutes of Health, the National Science Foundation, a Stanford CEHG Graduate Fellowship and the Howard Hughes Medical Institute.

Stanford's Department of Developmental Biology also supported the work.

ISM

Sibley

continued from page 1

Sibley's career had gained remarkable momentum in the years before his diagnosis. He'd been appointed to the role of assistant professor in 1999, and two years later received his first research project grant from the National Institutes of Health. The grant would support his work characterizing the genetic determinants of intestinal lactase persistence in humans. In 2004, he became a member of an NIH study section in which he participated in reviewing and recommending grants. The following year he was elected to the Council of the Society for Pediatric Research. In 2006, he became editor-in-chief of the *Journal of Pediatric Gastroenterology*, and that same year was promoted to tenured associate professor at Stanford. He went on to become chair of the growth, development and child health section of the American Gastroenterology Association. In 2010, his achievements in academic medicine were recognized by induction into the American Clinical and Climatological Association.

CRAIG HUEY PHOTOGRAPHY

Sibley received the Distinguished Service Award from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition in 2017.

"All those things were lining up, and if I had been able to continue at that pace healthwise, I was on a trajectory to continue as a leader in those different societies," Sibley said. "So that became a bit of a frustration, to have everything lining up perfectly, but then have the realization that I can't keep traveling to these national leadership meetings. It's just too hard on the body."

Lynne Olds, a research associate in the Sibley lab, recalled learning of his diagnosis around 2010. "Eric came to the lab to tell me he'd been diagnosed sometime before but had not made it public," Olds said. "My private reaction was profound sadness that this was happening to such a good man." Olds focused on making accommodations in the lab so that Sibley could continue working. "I wanted him to know that this was his lab, and whatever it took to make it possible for him to be physically in it would be done," she said.

Support from his colleagues helped Sibley focus on moving forward. "As his disability evolved, some of the procedures that he wasn't able to do I took on for him to some degree," Bass said. "Maybe the most remarkable thing is: It didn't really seem to change who Eric was. He addressed his disability, like, OK, how are we going to work around this? How can I keep going?"

Minority in medicine

Sibley's illness puts him among the 2 to 10 percent of practicing physicians with a disability, according to a 2005 study in the *American Journal of Physical Medicine & Rehabilitation*. Yet, as an African-American, Sibley was already well aware of what it meant to work as a minority in medicine. Only 4 percent of full-time medical school faculty identify as black or African-American, according to the Association of American Medical Colleges. Sibley attributes his perseverance in the discipline to his mentors who had paved the way.

Sibley's father, William Sibley, MD, practiced family medicine in South Los Angeles, not far from the family's home in the View Park-Baldwin Hills neighborhood. "View Park-Baldwin Hills was one of the few neighborhoods in the west side of Los Angeles where African-American professionals and entertainers could purchase homes with less realty discrimination," Sibley said. "We lived across the street from the jazz singer Nancy Wilson. And Ray Charles was two blocks over. Ike and Tina Turner were one block over." Sibley had two younger brothers. His mother, Mary Hall Sibley, managed the household.

Sibley attended the Harvard School for Boys, an elite private school in North Hollywood. "We were a class of 120, and there were four African-Americans, which was more than usual," Sibley said. "Two of them were from my neighborhood, and their fathers were also physicians."

Sibley entered Harvard University as a pre-med student. In his junior year, he served as president of Harvard's Percy Lavon Julian Science Organization, founded in 1972 to foster enthusiasm and interest in science, math and engineering among black students.

The founding faculty adviser of the organization was S. Allen Counter, PhD, a professor of neurology at Harvard and an influential mentor for Sibley. Counter died in 2017. "I had multiple meetings with Dr. Counter to talk about a career in science and medicine," Sibley said. "And he helped us arrange for prominent African-American scientists and physicians to come speak to our group."

> "It's inspiring to see someone who looks like me in a position I aspire to be in one day."

Sibley found mentors among his classmates, too. "The African-American upperclassmen had told me that, if you're pre-med, it was a good idea to try to get exposure to research and science," he said. Based on that advice, he spent his summers working in research laboratories at the National Institutes of Health and completed the research for his honors thesis in the molecular biology lab of Tom Maniatis, PhD, at Harvard.

After just three years at Harvard, Sibley graduated in 1982 with honors and went on to the MD-PhD program at Johns Hopkins. He was drawn to Johns Hopkins for many reasons, including the opportunity to interact with cardiothoracic surgeon Levi Watkins Jr., MD, who had been the first black student to attend and integrate Vanderbilt Medical School, and who went on to be the first surgeon to successfully implant an automatic heart defibrillator in a human patient.

At Hopkins, Sibley began to develop his research interests in gastrointestinal physiology. His doctoral thesis in biochemistry focused on insulin receptor gene regulation.

Making his mark at Stanford

Sibley completed his pediatrics residency at Harbor-UCLA Medical Center in 1993. His scientific pursuits ultimately drew him to a postdoctoral fellowship in pediatric gastroenterology at Stanford. Gary Gray, MD, professor of gastroenterology, was investigating the lactase enzyme protein and how the protein may be regulated differentially during maturation. But Gray's group was just beginning to explore regulation of the lactase gene.

"Besides being a trained pediatrician, Dr. Sibley had a PhD in molecular biology, an area that was crucial for our research," said Gray, now a professor emeritus. Gray's lab included technicians, a research associate and postdoctoral scholars. "Sibley immediately displayed exceptional leadership skills. He's just a spectacular human being — a humble, mature, quiet leader whom everyone was highly fond of."

Gray supported Sibley's application to the Robert Wood Johnson Foundation's Minority Medical Faculty Development Program. An award from the program helped secure Sibley's research time at 70 percent, which increased to 75 percent after he received a career development "K award" from the NIH shortly thereafter. Sibley went on to receive NIH research support for the next 20 years. Among other findings, Sibley's laboratory characterized and was the first to demonstrate functionality for the DNA polymorphism associated with lactase persistence in humans.

Kenneth Cox, MD, now a professor emeritus of pediatric gastroenterology, joined Stanford as the division chief of pediatric gastroenterology in 1995, when Sibley was still a fellow, and worked with him for more than two decades. "In our division, Eric was the scientist who was involved with very basic research, which was important for our division. He helped us get NIH funding for our fellowship program and mentored our fellows for their research and academics, and many of them chose academic careers because of that experience," Cox said. "Eric stands out as a model for the academic world in terms of being a basic researcher, a clinician and a mentor for other people who want to have that kind of career."

Changing the pace

By 2011, Sibley needed more than crutches to keep going. He began using a wheelchair, and had an automatic door installed in his office at the School of Medicine. Around the same time, he was appointed an academic advising dean at the school.

With about 475 students in the medical school at any one time, Sibley — one of four academic advising deans — supports between 110 to 120 students. "It ends up being possibly hundreds of one-on-one or group meetings with students over the course of the year, which is remarkable given that he's also doing research and clinical practice," said Neil Gesundheit, MD, MPH, professor of endocrinology and senior associate dean for medical education.

Sibley has a unique flair for supporting medical students, not only in routine academic, research and career guidance, but also when things aren't going well. "Sometimes students who are struggling in school begin to isolate themselves. We call it cocooning," Gesundheit said. "A student who is self-isolated because of not meeting a deadline starts to compound the problem by being ashamed that they haven't met the deadline. This makes matters worse."

Sibley has a way of reaching out to those students sympathetically and putting them at ease, Gesundheit said. "He'll say, 'I know it's hard for you to communicate back with me and maybe you're a bit ashamed of what's happened, but let's just start over and get things moving in a positive direction.' He's excellent at that, at really disarming a student and helping them address those kinds of issues."

With students who are the most vulnerable — those with physical or mental health challenges — Sibley found he could be the most helpful. "That's one area where my own health issues have made it a little bit easier for students to approach for the support they need," he said.

Gesundheit agreed. "He's vulnerable, and he's saying to you: If you're vulnerable, I can understand that and help you."

JANIE JOHNSTON

Sibley with his wife, Carol Somersille, an obstetrician-gynecologist, and their two children, Lauren Somersille Sibley and Carl Somersille Sibley.

In the spring of 2018, Maïté Van Hentenryck, a first-year medical student, and her roommate Claire Rhee launched a group for medical students with disabilities and chronic illnesses. A blood infection when Van Hentenryck was a baby had resulted in the loss of her right leg and other orthopedic issues. Their new group would need an academic adviser to meet official requirements, and Van Hentenryck, who had been randomly paired with Sibley as her academic adviser, knew just whom to ask.

"I reached out to Dr. Sibley to see if he'd like to be the group adviser," Van Hentenryck said. "And he responded immediately that he'd be really happy to." Rhee and Van Hentenryck were encouraged by Sibley's participation and what it held for the group's future. "I think he's going to be a tremendous resource for us," Van Hentenryck said.

Sibley had excelled in biomedical research, clinical care and education, but as a mentor and role model he provided something distinctive. **See SIBLEY, page 7**

Sibley

continued from page 6

Sibley could identify with students in ways that few other faculty could, and proved that there was a place for them in the highest ranks of medicine.

Mentoring the next generation

"It's inspiring to see someone who looks like me in a position I aspire to be in one day, especially because it's so rare," said Brian Boursiquot, a medical student at Stanford who is also African-American. "Dr. Sibley has helped me make important decisions about my academic pursuits and my choice of a clinical specialty."

Sibley's focus was also on advising fellows and aspiring physician-scientists in the pediatric gastroenterology department. Bass, who also worked closely with the fellows, heard from them about Sibley's engagement in their work. "He comes to their research talks, he asks them hard questions. He's fully engaged, and they're quite aware of that," Bass said.

One of those fellows was Zachary Sellers, MD, PhD, now an instructor of pediatric gastroenterology at Stanford. "Eric opened up his lab to me and really allowed me to use all of his equipment and supplies as if they were my own, which has been beneficial to me in having a platform to perform research that is specific to my interest in gastrointestinal complications that occur in cystic fibrosis," Sellers said. "I think in some ways it's a kind of pay-it-forward from the mentorship that he received early on in his career."

When she was new to Stanford Medicine's faculty, Aida Habtezion, MD, associate professor of gastroenterology and hepatology, was interested in applying for the Robert Wood Johnson program, just as Sibley had done. "It's nice when you find people who resemble you in many ways — as an African-American, a scientist and specifically a gastroenterologist — and who have been successful in the field that you are just starting. It gives you hope," Habtezion said. "And the things that they tell you, the encouragement they give you, the support in how you should position yourself, what applications you should look at, how you should improve your CV. These are some examples of things you get from them, and they are invaluable. Eric was a very important mentor who could guide me and give me advice, because he walked that path before me."

National recognition and responsibilities

Sibley's efforts as an adviser and mentor at Stanford soon earned him national responsibilities, as well. In 2016, he was named the inaugural director of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition's Mentoring Program for Investigative Junior Faculty. The program pairs assistant professors of pediatric gastroenterology with senior mentors at another institution to facilitate long-term mentorship affiliations. "In my communications with the leaders in the society, it is evident that Eric is deeply respected and admired — not just for his research, but also for his citizenship, generosity, teaching and mentoring," said Mary Leonard, MD, professor and chair of pediatrics.

MOSESE AHOMANA

In an effort to slow progression of his multiple sclerosis, Sibley receives a six-hour, twice-yearly monoclonal antibody infusion therapy, a pioneering treatment developed at Stanford.

Sibley has also had to deal with setbacks and challenges. In October 2016, while transferring from his bed to his wheelchair, he fell and broke his leg. "Turns out I have osteoporosis from sitting instead of using my bones," he said. "A lot of people who use wheelchairs get osteoporosis."

> "Eric Sibley has shown an indomitable spirit both personally and professionally."

The bone had to be set with a titanium rod that ran the length of his right femur. After his surgery, Sibley spent two weeks in a rehabilitation facility in Los Gatos. While he was there, Leonard called him to discuss two new departmental roles she hoped he would take: the inaugural associate chair for academic affairs, and liaison to the Office of Faculty Diversity and Development.

Sibley, who had learned that a physical setback didn't have to mean a professional one, was delighted to accept the positions.

Sibley's professional progress seemed to be the inverse of his disease progression. One year later, he received the Distinguished Service Award from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. This past spring, in his 25th year at Stanford, Sibley reached a long-awaited benchmark in his career: promotion to full tenured professor. He is the only African-American to begin his career as a postdoctoral scholar at Stanford Medicine and rise through the ranks to the highest faculty position.

"Eric Sibley has shown an indomitable spirit both personally and professionally," said Lloyd Minor, MD, dean of the School of Medicine. "Science can be unpredictable and at times discouraging, but Eric demonstrates that leading the biomedical revolution in precision health requires a revolutionary spirit. We at Stanford Medicine are very proud of his many accomplishments."

Even as he has become a nationally recognized mentor, he still remains an inspiration to his colleagues locally. For Bass, Sibley represents a standard of medical professionalism that he continually looks up to. "It's the core of what we're supposed to really be," Bass said. "That often gets lost in flashy technology, and although you can get distracted from it easily, it's about trying to help people, help them develop as much autonomy as they can, and being kind to fellow humans."

For Sibley, prevailing through adversity had a lot to do with those who'd cleared the path ahead of him, and his awareness that he could do the same. "There were times later in my career when there was no one like me in a role ahead of me, no one to advise or mentor me," he said. "So it was important to me to be that role model, to be a person students and colleagues with similar challenges could look to for guidance and encouragement." **ISM**

Opioids

continued from page 1

to a new study by researchers at Stanford and Duke.

For patients with shoulder, back or knee pain who did use opioids, early physical therapy was associated with a 5 to 10 percent reduction in how much of the drug they used, the study found.

Amid national concern about the overuse of opioids and encouragement from the Centers for Disease Control and Prevention and other groups to deploy alternatives when possible, the findings provide evidence that physical therapy can be a useful, nonpharmacologic approach for managing severe musculoskeletal pain.

"We asked ourselves, 'How can we address the pain that people are having, while not increasing their risk of needing opioids?'" said Eric Sun, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine at Stanford. "And what our study found was that if you can get these patients on physical therapy reasonably quickly, that reduces the probability that they'll be using opioids in the longer term."

> "Many guidelines suggest that physical therapy is an important component of pain management."

The study, from an analysis of private health insurance claims, was published Dec. 14 in *JAMA Network Open*. Sun is the lead author. Steven George, PhD, professor of orthopaedic surgery at Duke, is the senior author.

The researchers reviewed claims for outpatient and emergency room visits for the earliest instance of a diagnosis of shoulder, neck, knee or low back pain among privately insured, nonelderly adult patients.

The study screened out patients who had recently taken opioids by including only those who hadn't filled an opioid prescription within the prior year. The study also screened out patients with less serious pain by including only those who had visited a doctor for their condition within 30 days of their initial diagnosis and were given at least one opioid prescription within 90 days. The final sample consisted of 88,985 patients.

Fewer opioid prescriptions

After adjusting for co-morbidities, such as diabetes and hypertension, Sun and his colleagues found that the odds of patients filling an opioid prescription three months to a year after their initial pain diagnosis were lower if they had participated in at least one physical therapy session within 90 days of their diagnosis. The odds were reduced by 16 percent for patients with knee pain, 15 percent for shoulder pain, 8 percent for neck pain and 7 percent for lower back pain.

The findings, Sun said, could be helpful to clinicians in search of pain-management options that carry fewer health risks than opioids. Studies have shown exercise therapy, a component of physical therapy, reduces pain and improves function for some musculoskeletal conditions. Other studies have shown that patients with past prescriptions for opioid pain medication are at increased risk for overdose and misuse.

Less need for pain relief

"This isn't a world where there are magic bullets," Sun said. "But many guidelines suggest that physical therapy is an important component of pain management, and there is little downside to trying it."

Eric Sun

The study also measured whether early physical therapy was associated with a decreased need for opioids in the long term among patient who filled prescriptions. The researchers measured the quantity of opioids by converting prescribed amounts to oral morphine milligram equivalents.

They found, after adjusting for confounding factors, that patients who had undergone early physical therapy used 10.3 percent less opioid medication for knee pain; 9.7 percent less for shoulder pain; and 5.1 percent less for back pain in the period three months to a year after their diagnosis. There was no significant reduction for neck pain.

Physical therapy within three months of diagnosis also was associated with a decreased likelihood that patients with two of the conditions would chronically use opioids in the long term, according to the study. After early physical therapy, patients with knee pain were 66 percent less likely in the period three months to a year after their diagnosis to either fill 10 or more prescriptions or acquire a supply of opioid medication for 120 days or more. Patients with low back pain were 34 percent less likely to be chronic users if they had early physical therapy. There was no association between physical therapy and chronic opioid use among patients with shoulder or neck pain.

"The general consensus is that for musculoskeletal pain, opioids generally aren't a long-term solution," Sun said. "Aside from all the other side effects, even if the medication is doing well for you, it will have less and less effect over time as your body builds up a tolerance."

Other Stanford co-authors of the paper are Christopher Rishel, MD, PhD, a resident in anesthesiology, perioperative and pain medicine, and research analyst Jasmin Moshfegh.

Two other researchers at Duke also contributed to the study.

The research was supported by the National Institutes of Health and by internal Stanford funding.

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

Surgeon creates tools for assessing hands-on clinical skills

By Stephanie Bruzzese

When describing the inspiration for her life's work, Carla Pugh, MD, PhD, recalled her time as a medical student and surgical resident. "Before I could operate on a tumor, I needed to know how densely it was attached. A CT scan couldn't tell me — the only way I'd know was through my hands," said Pugh. "I realized I wouldn't truly learn how to diagnose with my hands just by watching my instructors, and I wanted to find a better way."

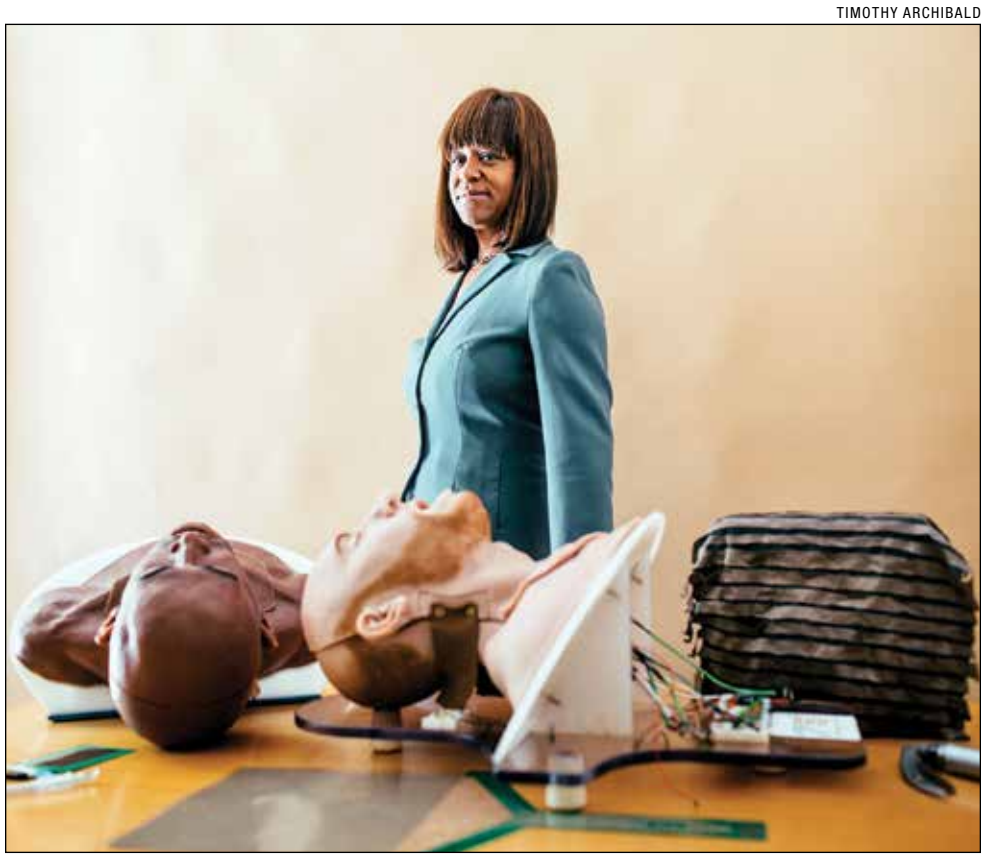
Today, Pugh is an international expert in the science of touch. She has created sensor technologies to quantify clinicians' hands-on skills and has combined those tools with educational concepts; together, they help medical students and residents learn to more effectively use touch when treating their patients.

After completing her surgical residency at Howard University, Pugh enrolled as a doctoral student in the Stanford Graduate School of Education, where she began to explore optimal training methods in the medical environment and to develop the sophisticated sensor, video and motion-tracking technologies that would be key to capturing haptic — or touch-sensing — information.

"It really all started at Stanford 17 years ago," said Pugh, who received a PhD in education in 2001 and now holds three patents on the use of sensor and data-acquisition technology to measure and characterize hands-on clinical skills.

Since returning in December 2017 — to take a dual role at Stanford Medicine as professor of general surgery and director of the Technology Enabled Clinical Improvement Center — Pugh has created collaborations across campus and beyond that are bringing the new field of touch technology and training to the next level.

TIMOTHY ARCHIBALD



Surgeon Carla Pugh, an international expert on touch sensor medical technology, displays mannequin heads and touch sensors — both plastic and fabric — that she and her team design and use to evaluate diagnostic and treatment skills.

On the technology side, for example, the Pugh lab has partnered with the Israel Institute of Technology to develop a fabric force-sensor bra that captures clinical data during a breast examination. Pugh is also exploring the creation of new touch-sensing tools with Stanford faculty members Allison Okamura, PhD, professor of mechanical engineering and an expert in haptics as well as virtual environments and simulators, and Zhenan Bao, PhD, professor of chemical engineering and of materials science engineering, who builds stretchable, flexible sensors.

Pugh is working with colleagues in the Graduate School of Education, including Dean Daniel Schwartz, PhD, and Karin Forssell, PhD, on the training half of the equation.

"In terms of the best approach to training students to use haptic data," she explained, "we need to know: How much of this should be learned while using your hands in context, or on a computer? Does this learning objective require a haptic display, or virtual reality? How much data can you collect during the process of care, right in front of the patient, and get real-time feedback that goes directly to a database?"

Pugh and her colleagues plan to engage industrial and systems engineers, social scientists and other experts in answering these critical questions about using the growing quantity of haptic data in training.

"Nationwide, trainees are telling us they want this information," said Pugh. "There's a lot more work to be done — but the audience is ready." ISM

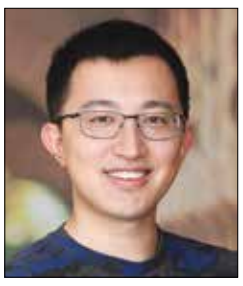
OF NOTE

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

Matias Bruzoni

Karl Deisseroth

Donald Frush



Zihuai He

Peter Kim

MATIAS BRUZONI, MD, was promoted to associate professor of surgery, effective Nov. 1. He directs the pediatric surgery fellowship and the Hispanic Center for Pediatric Surgery at Stanford Children's Health. His research and clinical interests include minimally invasive surgery in neonates, weight loss surgery in adolescents, surgical oncology and inflammatory bowel disease.

KARL DEISSEROTH, MD, PhD, the D. H. Chen Professor and professor of bioengineering and of psychiatry and behavioral sciences, was elected to the 2018 class of fellows of the National Academy of Inventors. Deisseroth pioneered optogenetics, a way of controlling cells with light, and hydrogel-tissue chemistry, a way of making biological tissues transparent and accessible for labeling and imaging biomolecules.

DONALD FRUSH, MD, was appointed professor of radiology, effective Nov. 1. His research centers on pediatric body computed tomography, including technology assessment, techniques for pediatric multidetector CT examinations, assessment of image quality, CT radiation dosimetry and risk communication.

ZIHUAI HE, PhD, was appointed assistant professor (research) of neurology and neurological sciences and of medicine, effective Nov. 1. His research focuses on statistical genetics and integrative analysis of -omics data, with an aim to develop methodologies for identifying and interpreting biological pathways involved in diseases, particularly neurological disorders.

PETER KIM, PhD, the Virginia and D.K. Ludwig Professor of Biochemistry, received an Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences from the Stanford Medicine Alumni Association. The award recognizes the lifetime achievements of School of Medicine alumni in the biomedical sciences. After discovering how proteins cause viral membranes to fuse with cells, a process required for infection by many viruses, Kim designed molecules that stop membrane fusion by HIV and pioneered efforts to develop vaccines based on similar principles. He is continuing his efforts to create vaccines, including against HIV.

Nicholas Leeper

Sergiu Pasca

Shannon Wiltsey Stirman

Adam Wang

NICHOLAS LEEPER, MD, associate professor of surgery and of medicine, received the Falk Catalyst Research Award from the Dr. Ralph and Marian Falk Medical Research Trust. The award program provides one year of seed funding to support high-risk, high-reward projects that address critical scientific and therapeutic roadblocks. The $300,000 grant will fund his study of nanoparticles to stimulate efferocytosis, the process of clearing dead and diseased cells from atherosclerotic plaque with the goal of preventing heart attack and stroke.

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, won the 2018 Daniel H. Efron Research Award from the American College of Neuropsychopharmacology. The award, which includes $1,500, recognizes outstanding basic research contributions to neuropsychopharmacology. He was recognized for pioneering a way to create balls of human brain cells that mimic the architecture of the cerebral cortex and for uncovering mechanisms of neuropsychiatric disorders.

Monte Winslow

Sherry Wren

SHANNON WILTSEY STIRMAN, PhD, was promoted to associate professor of psychiatry and behavioral sciences, effective Nov. 1. Her research focuses on developing and testing implementation strategies to facilitate the use of evidence-based psychosocial interventionsin routine care settings.

ADAM WANG, PhD, was appointed assistant professor of radiology, effective Nov. 1. His research focuses on developing technologies for advanced X-ray and CT imaging, including novel system design, model-based image reconstruction, spectral imaging and radiation transport methods.

MONTE WINSLOW, PhD, was promoted to associate professor of genetics and of pathology, effective Nov. 1. His research focuses on uncovering rules that govern tumor progression and metastasis, and discovering new therapeutic targets across the continuum of cancer progression, including the lethal metastatic stage.

SHERRY WREN, MD, professor and vice chair of surgery, was the inaugural recipient of the #SheForShe award from Women in Surgery Africa for supporting the development of female surgeons in the region. WiSA is a membership group that provides support to female surgeons, surgeons in training and medical students in the 14 member countries of the College of Surgeons of East, Central and Southern Africa. ISM