INSIDE STANFORD MEDICINE

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Anna Simos has devoted her career to preventing diabetes and caring for those who have it.

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Musician develops drug, changing career in process

By Kim Smuga-Otto

NORBERT VON DER GROEBEN

Finding an alternative remedy for her ulcerative colitis set Julie Saiki on a new and unexpected career path as a scientist and entrepreneurial drug developer.

Julie Saiki tried several violins from the Stanford Department of Music's collection until she found one whose sound was just right. But she kept herself from getting too attached. It was on loan — hers for as long as she was enrolled in lessons or performing with her chamber group at Stanford. She assumed returning the instrument would happen after she had earned a PhD in musicology. Instead, it happened because she switched degree programs.

Saiki will always be a musician, but now she is working toward a PhD in Stanford's Chemical and Systems Biology Program.

Saiki's plans for a doctorate in musicology were knocked off course after she was diagnosed with ulcerative colitis, a disabling inflammation of the colon. It wasn't the disease but the cure that sent her in a new academic direction. An herbal remedy put her symptoms into remission, and she went looking for a way to make it available to others. Despite having no science background, she enrolled in a course on drug development; successfully pitched her idea to SPARK, Stanford's drug development training program; and received approval from the U.S. Food and Drug Administration to begin a clinical trial. Each step brought her cure closer to patients, but the experience, and her success, caused her to re-evaluate her career.

"It was a big awakening," she said, upon realizing her curiosity and love of learning could be channeled to directly benefit others.

Saiki is a petite woman with delicate features. Her long, wispy hair falls over her eyes when she nods her head. But the hands that brush back the hair are taut and muscular. They move with precise intent, a consequence of years of violin training.

She doesn't remember a time when she didn't play, and in high school she set her sights on performing professionally. At Colgate University, in New York, her focus shifted to scholarship, and after graduating she spent a year as a Fulbright scholar researching Austrian chamber music. The Stanford Department of Music's strengths in Austro-German music made it a logical place to continue her studies. It would have been the perfect fit, if she hadn't gotten sick.

The disease and the cure

Her illness began with diarrhea, then blood in her stools and mild abdominal pains. She was diagnosed with ulcerative colitis her first year of graduate school, in the fall of 2008. The change came as a shock. Saiki, healthy her whole life, was taking up to 12 pills a day and visiting her doctor every

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Karl Deisseroth wins $3 million for work in creating optogenetics

By Bruce Goldman

Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences at Stanford, is the winner of a $3 million 2016 Breakthrough Prize in life sciences for his contributions to the development of optogenetics, a technique that uses light to control the behavior of cells and has proved especially invaluable in the study of nerve-cell circuits in the brain.

The award was presented Nov. 8 at a private black-tie, red-carpet ceremony in an airplane hangar at Moffett Field in Mountain View, California. Actor and television producer Seth MacFarlane, creator of the animated TV series *Family Guy*, was master of ceremonies for the event; singer and songwriter Pharrell Williams performed. Many Silicon Valley and Hollywood luminaries were in attendance. The Breakthrough Prizes, initiated in 2013, honor prominent individuals in the fields of life sciences, fundamental physics and mathematics. Deisseroth was among three Stanford scientists honored at this year's event.

STEVE JENNINGS / GETTY IMAGES

Karl Deisseroth speaks Nov. 8. at the 2016 Breakthrough Prize ceremony.

"The suffering of the mentally ill and the mysteries of the brain are so deep that, to make progress, we need to take big risks and blind leaps," Deisseroth said in his acceptance speech. "The members of my lab have taken a leap: borrowing genes from microbes to control the brain."

In an interview, Deisseroth said, "Optogenetics' biggest impact by

See DEISSEROTH, page 3

Immune cells' behavior before surgery linked to recovery time

By Kim Smuga-Otto

The behavior of a type of white blood cell can indicate how soon patients will be back on their feet after hip surgery, according to a study by scientists at the School of Medicine.

CHANAWIT / SHUTTERSTOCK

Stanford scientists hope to develop a diagnostic blood test that could indicate how soon a patient might recover from surgery.

The scientists plan to use the findings to develop a diagnostic blood test that patients can undergo before surgery.

U.S. doctors performed more than 50 million surgeries, including some 300,000 hip surgeries, last year. While indicators for negative outcomes — like organ failure, infection and death — have been extensively studied, indicators for

See RECOVERY, page 7

Study: Drug relieves symptoms of chronic depression in people who have insulin resistance

By Bruce Goldman

A drug that makes the body more sensitive to insulin helped to relieve symptoms of chronic depression in people resistant to the hormone, according to a study by researchers at the School of Medicine.

Natalie Rasgon

The 12-week, randomized, placebo-controlled study, published Nov. 18 in *Psychiatry Research*, involved patients whose symptoms of depression had failed to improve substantially, despite treatment, for at least six months leading up to the study's onset.

"This is the first placebo-controlled study to show the antidepressant benefits of treating unremittingly depressed patients with an insulin-sensitizing drug," said the study's senior author, Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences.

"The study is important," Rasgon said, "because it bears out a hypothesis we first advanced over a decade ago about the connection between insulin resistance — the body's inability to efficiently process glucose,

See DEPRESSION, page 7

Dangerous liaison: Bacteria, viruses in league, study finds

By Bruce Goldman

Scientists know a lot about bacteriophages, viruses that infect bacteria. Medical practitioners likewise understand the clinical dangers of biofilms: slimy, antibiotic-defying aggregates of bacteria and organic substances that can stick to the walls and inner linings of infected organs and to chronic wounds, making infections excruciatingly hard to eradicate.

But any link between bacteriophages and biofilms was unsuspected.

Now, in a series of experiments prompted by a chance discovery, School of Medicine investigators and their colleagues at three other research institutes have shown that a bacteriophage, or phage for short, is critical to the formation of biofilms by Pseudomonas, a bacterial pathogen behind numerous hospital-acquired infections, pneumonia cases and cystic fibrosis fatalities.

NORBERT VON DER GROEBEN

Paul Bollyky and his colleagues discovered that the viruses which infect bacteria are critical to the formation of biofilms involved in pneumonia and cystic fibrosis.

The experiments are described in a study published Nov. 11 in *Cell Host & Microbe*.

The study, the first to show that a phage can drive the formation of bacterial biofilms, is also the first to implicate any type of phage in causing chronic infections. The study also explains why biofilms can resist certain antibiotics, a discovery that could yield entirely novel therapeutic interventions.

The researchers studied members of a family of long, filamentous phages known as Inoviruses. Other related phage species of the Inovirus family probably contribute to biofilm formation by diverse bacteria, said Paul Bollyky, MD, PhD, assistant professor of infectious diseases at Stanford. Bollyky shares senior authorship of the study with William Parks, PhD, a professor of medicine at Cedars-Sinai Medical Center in Los Angeles.

Biofilms factor into 75 to 80 percent of hospital-acquired infections, such as those of the urinary tract, heart valves and knee-replacement prostheses, Bollyky said. "A familiar example of a biofilm is the plaque that forms on our teeth," he said. "You can brush twice a day, but once that plaque's in place you're never going to get rid of it."

Like all viruses, a phage can reproduce itself only by climbing into a cell — in this case, a bacterial cell — and commandeering its replicative machinery. Usually that's lethal to the invaded cell, because the viruses' offspring break out of the cell by puncturing its outer membrane, destroying the cell.

Leaving host cells alive

But Inoviruses don't do that. Instead, these long, thin viruses are extruded from the bacterial cell without causing damage. Indeed, as the study shows, in the presence of organic substances called polymers, they shelter the bacteria they've infected by forming goopy lattices — biofilms — able to repel or sequester electrically-charged small molecules, including many drugs.

Members of the Inovirus family of phages infect a broad class of bacteria, encompassing Escherichia (for example, *E. coli,* which can aggregate into treacherous biofilms) as well as Pseudomonas. One Pseudomonas species alone, *P. aeruginosa*, accounts for about 10 percent of all hospital-acquired infections, many chronic pneumonia cases, a large fraction of wound infections associated with diabetes and much of the air-passage obstruction that afflicts cystic fibrosis patients.

Serendipity played a major part in the revelation of a phage's role in bacterial biofilm generation. Patrick Secor, PhD, a senior fellow in microbiology at the University of Washington and the lead author of the study, was growing *P. aeruginosa* in culture and wondered if a substance called hyaluronan might be a good energy source for the bacteria. To test this, Secor mixed hyaluronan into the culture medium. Before his very eyes, a biofilm sprang up and spread rapidly through the culture.

Hyaluronan is a polymer — a large organic molecule composed of many repeated subunits — and one of many made by living creatures. Other examples include DNA and mucin, the main constituent of mucus. A prominent feature of cystic fibrosis is the presence of high levels of extremely viscous mucus in the sputum.

Cystic fibrosis, a genetic disease affecting one in 2,500 people, is deadly chiefly because of biofilms formed by *P. aeruginosa*, said Bollyky. "These biofilms fill up all the air spaces, and antibiotics can't seem to penetrate them," he said. "So, patients eventually succumb to infectious pneumonia."

By adulthood, virtually all cystic fibrosis patients are colonized by P. *aeruginosa*, Bollyky said. Resulting biofilms eventually render their sputum extremely viscous, sticky and tough to get rid of short of a lung transplant, he said.

Teaming up

Bollyky, a polymer-chemistry expert, is a good friend of Secor's, and they began working together. With their associates, they demonstrated that several polymers, including bacterial DNA and the mucin of cystic fibrosis patients, could trigger biofilm formation in *P. aeruginosa* — but only if the Inovirus was present.

"The long, filamentous phages made by the bacteria interact with these polymers to form orderly structures that help biofilms stick to surfaces and resist removal," Bollyky said. "I always assumed that biofilms were chaotic networks of polymers and bacteria that look like the hairball plug you pull from the bottom of your shower drain. We were surprised to see that actually, in the presence of these phages, biofilm architecture is more like a crystal than a hairball. That higher-order organization makes these biofilms much more tenacious and formidable."

Examining sputum from CF patients, some infected with *P. aeruginosa* and others not, the investigators identified phage particles in the infected patients' sputum. Adding phage particles to uninfected sputum samples induced the rapid generation and spread of highly organized biofilms in those samples.

Further experiments may also explain why certain antibiotics work better than others against chronic infections. "The same physical properties that allow phage to organize biofilms also make them very efficient at sticking to antibiotics and trapping them within the biofilm. They never get close to the bacteria," Bollyky said. "These phages may be one reason why chronic infections with *P. aeruginosa* require long treatment courses of high-dose antibiotics." Phages are particularly good at binding some antibiotics, such as tobramycin, penicillin and azithromycin, while others, such as ciprofloxacin, are able to pass right through, the researchers found.

The researchers documented similar biofilm dynamics using other bacterial species, including *E. coli*. All in all, bacteria carrying similar phages are responsible for about half of all hospital-acquired infections, Bollyky said.

"If these findings can be validated, it could open the door to entirely new therapeutic targets for combatting hospital-acquired infections, complications of cystic fibrosis and much more," Bollyky said. His group is exploring approaches to target phages therapeutically, such as chelating agents that might disrupt biofilms' integrity and antiviral compounds that prevent Inovirus family members from reproducing.

Other Stanford-affiliated co-authors are undergraduate Ethan Katznelson; graduate student Johanna Sweere; medical student Daniel Lazzareschi; postdoctoral scholars Andrey Malkovskiy, PhD, and Michael Birnbaum, PhD; and Jayakumar Rajadas, PhD, lecturer in the Department of Medicine.

Researchers from the Benaroya Research Institute and the University of Washington, both in Seattle, and the California Institute for Medical Research, in San Jose, also contributed to the study.

The study was funded by the National Institutes of Health and the Cystic Fibrosis Foundation.

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

Team creates repository of advice on ethical research practices

By Kris Newby

A team of bioethicists from across the nation has developed a standardized approach to collecting and sharing advice on conducting ethical human-subject research.

At its core is a template to help bioethicists structure ethics consultations so that resulting knowledge can be shared in a centralized, privacy-protected database. This online resource, which is accessible to contributing members of the Clinical Research Ethics Consultation Collaborative, aims to help them provide better guidance to researchers, educators and regulators in rapidly evolving research areas such as genetics and social-media data collection.

The effort was led by Mildred Cho, PhD, of the Stanford Center for Biomedical Ethics, and Benjamin Wilfond, MD, of the Seattle Children's Research Institute and University of Washington.

The proposed framework was published in the August issue of *Clinical and Translational Science*.

"Our bioethics consortium has learned a great deal from the complex ethics consultations that we've been providing since 2005," said Cho, professor of pediatrics and of medicine. "Now we have a strategy for sharing these best practices with others, to provide moral and legal guidance to researchers across the country and to better inform policymakers on evolving ethical gray areas."

This is one of several initiatives spearheaded by the Clinical Research Ethics Consultation Collaborative, a group of almost 50 bioethicists who provide free or low-cost ethics consultations across the United States. Members share perspectives on novel or complex ethical issues, participate in collaborative consultations, and contribute to cases and commentaries in the *American Journal of Bioethics*.

The group's recently expanded website includes a publicly available collection of challenging ethics case studies in the areas of social science research, clinical trials, genetics, pediatrics, research misconduct and surrogate decision making. The site also includes information on how to participate in educational webinars and collaborative case discussions.

The collaborative is supported by Spectrum, the Stanford Center for Clinical and Translational Research and Education, and other members of the Clinical and Translational Science Award consortium, and is funded by the National Center for Advancing Translational Sciences.

For more information on the collaborative, visit https://www.ctsabioethics.org.

To request an ethics consultation at Stanford, visit https://med.stanford.edu/bioethics/service/bedside.html.

To request a consultation through the collaborative, go to https://www.ctsabioethics.org/consultations/request-a-consult/. ISM

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STANFORD MEDICINE

Nine professors elected fellows of AAAS

Nine Stanford faculty members — eight from the School of Medicine and one from the School of Humanities and Sciences — have been named fellows of the American Association for the Advancement of Science. AAAS members are elected as fellows by their peers for meritorious efforts to advance science or its applications.

KARLENE CIMPRICH, PhD, professor of chemical and systems biology, was elected for contributions to the understanding of genome maintenance, particularly for elucidating molecular mechanisms of DNA damage signaling and cellular sources of genome instability. Her research has illuminated the role of RNA and certain enzymes called endonucleases in causing DNA damage.

GERALD CRABTREE, MD, professor of pathology and of developmental biology, was elected for his work on the interaction between the signaling pathways and genetic circuits regulating embryonic development. Crabtree, who holds the David Korn, MD, Professorship in Pathology, studies the role of chromatin-regulatory complexes, protein complexes that work to keep DNA tightly condensed, in development and human cancer.

STEPHEN GALLI, MD, professor of pathology and of microbiology and immunology, was elected for his work elucidating the role of basophils and mast cells in allergy, infectious disease and inflammation. Galli, the Mary Hewett Loveless, MD, Professor, investigates the roles of mast cells and basophils in conditions such as asthma and atopic dermatitis, as well as immunological mechanisms that underlie the development of severe allergies.

JOHN HUGUENARD, PhD, professor of neurology and neurological sciences, was elected for contributions to the fields of basic and translational epilepsy research, particularly in the discovery and development of novel pharmacological and optogenetic therapeutic approaches. Huguenard studies and models circuits in the thalamocortical system of the brain, which is implicated in certain forms of epilepsy.

STEVEN KAHN, PhD, professor of physics, was elected for his contributions to X-ray astronomy through observations made with XMM-Newton's Reflection Grating Spectrometer, and for ongoing leadership of the Large Synoptic Survey Telescope project. Historically, his efforts have been concentrated in X-ray spectroscopy of astrophysical sources, but more recently Kahn, who is the Cassius Lamb Kirk Professor in Natural Sciences, has focused on experimental cosmology.

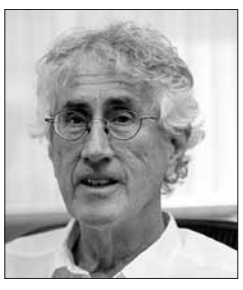
CALVIN KUO, MD, PhD, professor of hematology, was elected for contributions to the fields of angiogenesis, stem cell biology and cancer modeling, particularly for the discovery of novel molecular mediators and organoid methods. Kuo, the Maureen Lyles D'Ambroglio Professor, develops methods to grow tissues and tumor samples to create therapies for cancer patients and discover cancer-related genes.

BEVERLY MITCHELL, MD, professor of oncology and of hematology, was elected for contributions to the field of hematology and oncology, particularly for studies on the roles of purine metabolism and factors regulating ribosomal RNA synthesis in promoting cancer growth. Mitchell, who is the George E. Becker Professor in Medicine, develops new therapies for hematologic malignancies and directs the Stanford Cancer Institute.

HUGH O'BRODOVICH, MD, professor and chair of pediatrics, was elected for his work in pulmonary and critical care medicine, particularly for studies of the physiology and pathogenesis of respiratory distress syndrome and bronchopulmonary dysplasia. O'Brodovich, who holds the Arline and Pete Harman Professorship for the Chair of the Department of Pediatrics, investigates why some newborns get lung disease and others don't.

THOMAS RANDO, MD, PhD, professor of neurology and neurological sciences, was elected for contributions to the field of stem cell biology, particularly for pioneering work using heterochronic parabiosis to study stem cell aging. Rando studies the signaling pathways involved in stem cell quiescence, proliferation, self-renewal and aging, as well as the cells' role in muscular dystrophy. ISM


Karlene Cimprich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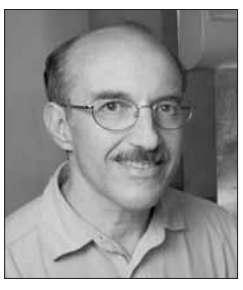
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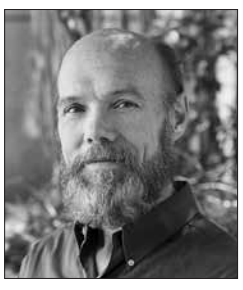
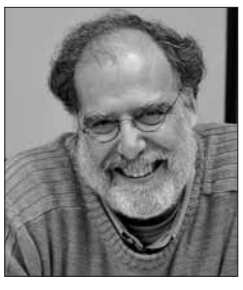

John Huguenard


Steven Kahn


Calvin Kuo


Beverly Mitchell


Hugh O'Brodovich


Thomas Rando

National Cancer Institute names 3 researchers outstanding investigators


Steven Artandi

The National Cancer Institute has awarded three School of Medicine researchers outstanding investigator awards.

The awards support long-term projects of "unusual" potential with up to $600,000 per year for seven years. Stanford's recipients are Steven Artandi, MD, PhD, professor of medicine and of biochemistry; Laura Attardi, PhD, professor of radiation oncology and of genetics; and Amato Giaccia, PhD, professor of radiation oncology.

Artandi researches how tumors acquire immortal growth properties, a fundamental characteristic of human cancer. He and his lab team hope to develop therapeutic approaches to reverse the process, without which cancer cells cannot persist.


Laura Attardi

Attardi plans to use the award to understand how a tumor suppressor protein called p53 inhibits pancreatic cancer development, and how mutant versions of the protein can promote the disease.


Amato Giaccia

Giaccia will investigate the role of lipid metabolism in cancer and seek to identify ways this information could lead to new therapeutic approaches targeting solid tumors.

Over 40 investigators from around the country received the outstanding investigator awards, which were presented for the first time this year. ISM

Deisseroth

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far has been in enabling thousands of discoveries about how neural circuits control behavior. I hope this technology will continue to be used to discover many more principles of nervous-system function, in health and in neurological and psychiatric disease."

Deisseroth joined this year's other Breakthrough Prize winners in giving lectures Nov. 9 at a symposium at the University of California-Berkeley. He is one of five prizewinners in the life-sciences category, each of whom received $3 million in unrestricted funds.

Optogenetics is a breakthrough laboratory methodology that allows scientists to precisely manipulate nerve-cell activity in freely moving animals to study their behavior. Optogenetics uses light to control the messages traveling along selected nerve cells and pathways.

First, genetic-engineering techniques are employed to insert genes for photosensitive proteins called microbial opsins into the nerve cells of living animals. The genes are bioengineered so that the opsins coat the surfaces of designated nerve cells. As a result, signaling by these selected nerve cells can be activated or inhibited by pulses of laser light that, at the flip of the experimenter's switch, are transmitted by a hair-thin optical fiber implanted in a laboratory animal's brain. Scientists can observe the effects of these manipulations on the animal's behavior and deduce the role played by particular nerve cells, relays and circuits.

"The human brain has been called the most complicated object in the universe, but that hasn't daunted Karl's quest to understand it," said Lloyd Minor, MD, dean of the School of Medicine. "If anything it seems the challenge has inspired him to develop techniques to see inside this most important of black boxes. This passion to understand the mind, combined with his intelligence and creativity, led to his pioneering role in creating optogenetics."

Psychiatrist and bioengineer

Minor also noted that Deisseroth is a practicing psychiatrist who sees patients as well as a bioengineer, which "exemplifies Stanford Medicine's unique ability to bring together research, patient care and teaching."

Deisseroth, who is the D. H. Chen Professor and a Howard Hughes Medical Institute investigator, has won numerous prizes for his pioneering work, most recently the prestigious Albany Award and the National Institutes of Health's Lurie Prize in Biomedical Sciences, both awarded this year. He serves on the advisory committee of the White House BRAIN Initiative.

In total, close to $22 million was awarded at the ceremony. There were seven $3 million awards, one of which will be split among some 1,300 physicists; $500,000 split among eight early-career researchers; and $400,000 to a high school student. The two other Stanford researchers honored at the event received New Horizons in Physics Awards, each of which is paired with a $100,000 prize. Xiao-Liang Qi, PhD, an associate professor of physics, was recognized for "outstanding contributions to condensed matter physics, especially involving the use of topology to understand new states of matter." Leonardo Senatore, PhD, an assistant professor of physics, was honored for his "outstanding contributions to theoretical cosmology." The prizes, funded by the Milner Foundation, go annually to promising junior researchers who have already produced important work.

"The Breakthrough Prize recognizes contributions to science that will inspire and encourage others. The innovative work of professors Deisseroth, Qi and Senatore indeed ignites that thrill of discovery as they seek to solve the greatest mysteries within our vast universe, and within the universe of our brain," said Stanford President John Hennessy, PhD. "Karl Deisseroth's pioneering work in optogenetics proves the value of tackling deep problems across disciplines. And we are immensely proud that two physics faculty members, still at the outset of their promising careers, have been recognized as catalysts in their field. On behalf of the entire Stanford community, I congratulate them all and thank them for their brilliant example."

The annual Breakthrough Prizes are funded by grants from the Brin Wojcicki Foundation, established by Google co-founder Sergey Brin and 23andMe founder Anne Wojcicki; Mark Zuckerberg's fund at the Silicon Valley Community Foundation; Alibaba founder Jack Ma's foundation; and DST Global founder Yuri Milner's foundation. Recipients are chosen by committees comprised of prior prizewinners. ISM

VANTAGE POINT

one in an occasional series of essays written by faculty and staff

It's time to talk honestly about dying

By Karl Lorenz

Sometimes, it doesn't take much to communicate well. One of my earliest experiences as a palliative care doctor was at the bedside of a man with advanced cancer who was having trouble eating and keeping up his weight. A feeding tube was planned for the next day, but it wasn't going to help. Although no one had voiced it, we knew the cancer was getting worse. A gentle acknowledgement of that fact allowed us to recognize that death was near, and a moment of shared grieving gave us time to rethink the "more is better" refrain we're so used to. He decided to forgo the tube for a chance to go home, where he died some weeks later.

LIGHTHUNTER / SHUTTERSTOCK

Although language is one of our most fundamental faculties, we can't be sure of clear communication when we are ill: What do we have? What's likely to come next? What are our options? How much time is left? As it turns out, research shows that we often conspire with our doctors to suppress emotionally troubling conversations. Recent research suggests that in the best case we might expect to see good, clear communication soon after a metastatic cancer diagnosis less thane one-fifth of the time. In general, communication about end-of-life care in the United States seems to have gotten worse, instead of better, in recent years.

We need to be able to "see" communication between patients and providers in order to improve it. We've long relied on doctors' notes in medical records to identify when doctors and patients discuss goals for care, and notes remain helpful because effective communication has to convey information to all kinds of different people — oncologists, nurses, general practitioners, hospitalists, palliative care specialists — over a long period of time. However, the ability to analyze and search text or even use speech analysis to characterize conversations with patients and families could prove newly useful in identifying and making sense of all this information.

We also need to encourage more communication, of higher quality. Medicare recently proposed paying doctors for end-of-life planning, including the lengthy and repeated conversations that sometimes entails. One of the biggest oversights in end-of-life care is the need to ask patients or their families if they have had helpful end-of-life conversations. Health-care systems that do measure this tend to find significant gaps in quality, and the much larger Medicare system shouldn't let doctors off the hook. Payment might help, but simply creating more advance directives won't foster better end-of-life care unless we ensure good, high-quality discussions.

Karl Lorenz

While we need professionals who communicate well, there's plenty of evidence that doctors need not be the only ones for the job. Nurses, social workers and spiritual advisers play critical professional roles, and lay advocates are another consideration. Dr. Manali Patel, an investigator at Stanford University, is testing the idea of using paid or volunteer workers to check in on and advocate for the sick, helping to bridge the community-to-professional gap. Most of what supports us in health or sickness depends on what happens outside the cloistered clinics and hospitals we visit. In all cases, teamwork is key to effectively using our currently thin professional resources.

Similarly, health-care systems need to make sure that the voices of patients and their families are heard. Many health-care systems are emphasizing "patient-reported outcomes" communications from patients about their own health, on their own terms. Just as important is the idea of giving patients and families a direct voice. Why aren't they included when we deliberate budgets for hospital improvements? Does the C-suite hear the stories that patients and families tell at end of life?

Finally, we must have to be sure that our wishes are respected, no matter what they are. In *Wit*, Margaret Edson's 1999 Pulitzer Prize-winning play about a poetry professor overcome both by her advancing ovarian cancer and her physicians' intellectualization of the situation, the audience experiences profound distress when the character's oncologist ignores her dying wish for comfort. The play serves as a powerful example that those who provide for our health should provide comfort and support when and where we need it.

Some states are creating electronic registries so that our preferences can be accessed anytime, anywhere they are needed, like when we visit an emergency department. Primary-care and specialist clinicians such as oncologists need some basic skills in promoting comfort, and health-care providers should offer palliative care and hospice when patients and families need or request more advanced support.

Almost all of us will eventually become caregivers or patients at the end of life, but we won't overcome the challenges that ensue unless we acknowledge and forthrightly address the pain and fears that the end of life can bring. Policymakers, insurance payers and the wider public will all reach the same fate, and the journey isn't always easy. Knowing that we're all in this together, can we find the will to make honest words at the end of life more routine? **ISM**

Karl Lorenz is a professor of medicine at the School of Medicine and the section chief for the Veterans Health Administration-Stanford programs in palliative care. This piece was originally published Oct. 29 in The Washington Post.

Study: Ethnicity does not predict end-of-life care patients want

By Tracie White

Ethnicity does not predict the type of end-of-life care people want, according to a study by researchers at the School of Medicine

"There is so much generalization and stereotyping by physicians about how ethnic minorities want *everything* done, irrespective of how effective these treatments might be at the end of life," said VJ Periyakoil, MD, a clinical associate professor of medicine at Stanford and lead author of the study, which was published online Nov. 18 in the *Journal of Palliative Medicine*. "I decided that we needed to go into their communities and ask them what they want."

The study found that ethnic minorities want conversations with their physicians about quality end-of-life care, but numerous barriers, including poor communication and finances, often get in the way.

Helena Kraemer, PhD, professor emeritus of biostatistics in psychiatry, is senior author of the study.

The researchers interviewed 315 people of multiethnic backgrounds — including 117 white Americans, 38 African Americans and 160 Asian Americans — over the age of 50 from cities across the San Francisco Bay Area. They found that all participants valued high-quality end-of-life care. A majority, 61 percent, said there were barriers to receiving high-quality care for members of their ethnic group.

The inequalities in health care that occur across ethnic and socioeconomic groups persist well into end-of-life care, the study said, with seriously ill ethnic minority patients being disproportionately affected by poor-quality care.

"In reality, it is more of a socioeconomic issue than an ethnic issue," said Periyakoil, an expert in palliative and end-of-life care.

Education level tied to participant responses

For the study, medical interpreters accompanied the Stanford researchers into community-based senior centers in Fremont, Palo Alto, San Francisco, San Jose and Walnut Creek to help conduct interviews in the participants' preferred language. In addition to English, interviews were conducted in Spanish and five Asian languages — Burmese, Hindi, Mandarin, Tagalog and Vietnamese.

The 191 participants who reported barriers to getting quality end-of-life care were asked to describe the biggest barriers, which were, in order of how often they were cited: finances and health insurance; physician behavior; communication problems with doctors; family beliefs; health system barriers; and cultural/religious barriers.

A comparison of the various ethnic groups interviewed showed no significant differences in how they ranked these barriers.

VJ Periyakoil

But education level was found to have a significant influence. Participants with no formal education found financial issues to be most challenging, followed by a communication chasm between doctors and patients. Participants with any other level of education (elementary, high school or more) identified doctor behaviors as being the biggest barrier.

The majority of participants ranked lack of finances and inadequate medical insurance as the biggest barrier, according to the study.

"Lack of basic health access continues to plague the poorest in the nation," the study said, adding that 43 percent of all Americans reported cost-related problems in getting needed health care.

Communication barrier

Poor communication with physicians was the second-most-common barrier reported by participants. They felt that "doctors were just too busy to initiate conversations," and that "doctors were either unaware of, or insensitive to their cultural/spiritual needs," causing patients to shy away from "intensely personal" end-of-life conversations, the study said.

"If a patient says, 'I'm praying for a miracle,' there's the concern that the doctor might say something insensitive," Periyakoil said. "You can't tell patients that miracles are unlikely to happen or question their faith and beliefs. Physicians need to be sensitive to religious and cultural beliefs and support them to the extent possible."

Participants also reported an inability to understand medical terminology, language barriers and family members with differing beliefs about death and dying.

"Most people don't know that at some point most of us will lose our ability to make health-care decisions at the end of life," Periyakoil said. When this happens, a family member is usually required to step in as a proxy decision-maker.

"Making medical decisions for a loved one takes mental fortitude and a deep understanding of the patient's values and preferences for care" Periyakoil said. "It's a profound responsibility choosing whether a person dies at home or in a hospital, what types of treatments to attempt or forego, and when to limit or withdraw burdensome interventions and allow a natural death. I've seen far too many families split apart due to the trauma of this decision making. In fact, the only right decision is what the patient wants."

Providing culturally competent end-of-life care is becoming more essential as the United States is poised to become a nation whose majority population is made up of minorities by 2044, the study said.

The fragmented health system, which doesn't train doctors to communicate effectively with their patients about end-of-life choices, is the underlying larger problem that is in need of an urgent solution, the study said.

Eric Neri, database manager and analyst at the Stanford Medicine Center on Stress and Health, is a co-author of the study.

The research was supported by the National Institutes of Health and the Department of Veterans Affairs.

Stanford's Department of Medicine also supported the work. **ISM**

For diabetes educator Anna Simos, work is personal

By Sara Wykes

Anna Simos had always been the healthy one in her family — never a candy eater, she said — but, at 15, she was diagnosed with the traditional family illness: diabetes.

She remembers that day quite clearly. "My grandmother and uncle both had Type 1 diabetes and my father was diagnosed with Type 2, so when I was diagnosed, I knew what it meant for my life moving forward," she said. "It was sobering, and I knew there was no easy way out. I remember that first day when the doctor brought in a syringe with insulin and told me to give myself a shot. I asked him, 'How many times will I have to do this? Every day?' 'Probably four to six,' he said. I was not happy."

Over the intervening 33 years, and through one pancreas and two kidney transplants, Simos, who received much of her medical care at Stanford Health Care, has learned how to balance her diet, lifestyle, medications and essential medical equipment to live a life with Type 1 diabetes. By the time she was a college student, she had begun to think about what she could do to help others with the disease. "I had figured it out for myself, but as I began meeting others with diabetes, I decided I should do something with this on-the-job training," she said.

In the mid-1990s, she earned master's degrees in public health and in epidemiology, with a focus on diabetes, so she could start to educate others about the challenges of the disease that had touched her life. She joined Stanford as a certified diabetes educator and diabetes clinical research coordinator in 2000.

'Epidemic levels'

The worldwide statistics on diabetes are staggering. The Centers for Disease Control and Prevention estimates that 387 million adults have a form of diabetes — either Type 1, in which the pancreas does not produce insulin; Type 2, in which the body may both underproduce and resist the effects of insulin; or a Type 2 variant that develops after organ transplantation. About 86 million American adults, more than 1 in 3, are prediabetic. Prediabetes, defined by blood sugar levels that are above normal but not high enough for a Type 2 diagnosis, increases the risk of heart disease, stroke and Type 2 diabetes.

"Diabetes and prediabetes are at epidemic levels," Simos said. Those numbers drive her efforts. By focusing on education and prevention, Simos hopes she can halt people's progression to Type 2 diabetes and stave off complications in patients who already have the disease before the worst of its consequences take root. "We want to help prevent the transplant, the amputation and the blindness that can result from poorly managed diabetes — all things we can treat and turn around with the right care," she said.

On Nov. 13, Simos saw one of her combined personal and professional goals met: Stanford Health Care's first Diabetes Prevention and Wellness Health Fair. The free, public event brought together 15 nonprofit organizations and vendors, clinicians from Stanford Health Care and Stanford Children's Health, and other diabetes education experts to provide free risk assessments, updates on diabetes care technology, food demonstrations and nutrition education. Keynote speaker Charlie Kimball — an IndyCar driver who is living with diabetes — talked about how he meets the everyday challenges of the disease. "Everyone's coming together for the first time," Simos said shortly before the event. "You're going to learn something if you come, because it's not just about diabetes — it's also about prevention and how you can live a full life with the disease."

The Diabetes Prevention and Wellness Health Fair allowed Stanford's diabetes clinicians to share their knowledge, accumulated over decades of caring for patients and bolstered by Stanford Medicine research. In recent years, Stanford scientists have uncovered key molecular pathways for insulin-producing cells and a substance whose buildup in the pancreas is an essential precursor to Type 1 diabetes development.

Walking in patients' shoes

Simos has endured many of diabetes' long-term effects, including vision loss and nerve damage to her hands, feet and stomach. The people she educates about their disease come to know that "she walks in the same shoes," said one of her patients, Ed Gray. "She teaches from experience."

Gray, diagnosed with Type 2 diabetes at age 18, is now 49. Over time, he has withstood the disease's most predictable consequences: a triple coronary bypass, a kidney transplant and blindness. The transplant requires him to take certain medications that make it more difficult to control his blood sugar. When one of his feet became infected and would not heal, as often happens with diabetes, he faced the possibility of amputation. Simos and Gray knew that an insulin pump could better regulate his blood sugar, but Gray's inability to see made that option challenging. "Anna understood that independence is important to me," said Gray, who works full-time as a director at a Silicon Valley digital video production software company. "She advocated for me and worked on her own time to discover the combination of devices that would work best for me and my condition."

With the approval of his Stanford Health Care doctor, clinical associate professor of medicine Marina Basina, MD, Simos trained Gray to operate the devices by touch. "It took lots of patience from all of us," Simos said. And it worked: Gray's glucose levels have never been controlled so well. "I feel better than I ever have," Gray said. Added Simos, "The bonus is that he still has both of his feet."

> **"She teaches from experience."**

This kind of dedicated care is a Simos trademark. "She provides emotional support and close follow-up, which extends beyond regular work hours when needed," said Basina. "She also can coordinate care between inpatient and outpatient, so patients don't get lost to continuing care following hospitalization."

Simos is leading an effort to have Stanford Health Care's diabetes program certified by the National Credentialing Board of Diabetes Educators. She also serves as a liaison among the internal medicine, endocrinology and transplant programs. "That improved coordination will support the standardized diabetes care at Stanford," said Basina.

Simos also works with registered dietitians such as Patsy Obayashi, MS, who is dedicated to diabetes care for people who have received a liver, kidney or pancreas transplant. Post-transplant health requires lifelong maintenance in a multitude of areas, from diet and physical activity to infection prevention and stress reduction. Having uncontrolled diabetes — whether triggered by the transplant or pre-existing — threatens not only overall health, but also the transplanted organs. "One of the reasons we started the post-transplant diabetes program is because it wasn't good enough just to tell people to pay attention to their diabetes and hear them say, 'Of course,'" Obayashi says. "We wanted to provide them with the needed tools and practical recommendations on how to do that."

NORBERT VON DER GROEBEN

Ed Gray credits diabetes educator Anna Simos with developing strategies for managing his diabetes that are tailored to his needs and lifestyle.

'People are beautiful puzzles'

Simos understands that even well-conceived tools and practical recommendations cannot be delivered like marching orders. She strives to understand what might work for each of her patients. "You cannot judge a person's inability to comply with care requirements," Simos said. "You can't give up on them. People are beautiful puzzles and, piece by piece, we put them together."

Take the puzzle of Breanna Sevy, a UC-Berkeley student who wanted to study abroad. Although she had been diagnosed with Type 1 diabetes when she was 4, Sevy had never wanted (or learned) to give herself the insulin shots she needed on a daily basis. For years, she had others do it for her. When she transferred from pediatric diabetes care to the adult program at Stanford Health Care, she became Basina's patient and Simos', too. And she was wary of finger-pointing from her clinicians about what she was doing right and wrong when it came to her diabetes care. "Most diabetes doctors will say, 'You're doing this wrong, and you're going to die,'" Sevy said.

Simos started Sevy's treatment slowly. She recommended Sevy try to use an insulin pump to manage her diabetes, since the device would free her from the need to give herself the daily injections she feared. Even though the insulin pump would eliminate the shots, Sevy would still have to prick her finger for blood samples several times a day. Knowing this was something Sevy also found challenging, Simos asked Sevy to start by trying to do it just once a week. Sevy could handle that, and she worked her way up slowly to three to four pricks a day. This incremental approach brought Sevy to a place where she could manage and control her diabetes and confidently make that study trip to Europe. "Anna is the pivotal reason I am able to go on this trip," Sevy said.

That's the kind of success Simos is happy to see. What she also wants — and the Diabetes Prevention and Wellness Health Fair was a first step — is to teach more people about the risks of poorly managed diabetes and to lobby for more diabetes educators wherever health care is available. "We need more people educated about the disease," she said. "It's moving so fast. If we can just get people to start thinking about their risk factors, we can take a different approach to diabetes: prevention." ISM

Sara Wykes is a writer for the Stanford Health Care communications office.

Drug

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two weeks. The disease took a mental toll, as well.

"I started to care less about my music; it didn't seem as important when my body wasn't functioning properly," Saiki said.

Ulcerative colitis often strikes people in their 20s. In about half the cases, the disease responds to the drug 5-aminosalicyic acid, inflammation recedes and patients live symptom free. In those who don't respond, stronger treatments, such as immunosuppressants, are brought into play. Uncontrolled ulcerative colitis increases the risk for colorectal cancer and, for the 10 percent of patients who do not respond to any treatments, surgical removal of the colon and rectum is required.

Patients and their doctors usually try 5-aminosalicyic acid with corticosteroids before moving on to immunosuppressants, which increase patients' risks for infections and some cancers. In addition to standard medications, Saiki also tried changing her diet by eliminating oily and sugary foods and by taking probiotics. Nothing worked. Months passed, and she wasn't getting better.

When her father mentioned an herbal remedy he'd read about, she decided to give it a try. After tracking down a supplier, she received the herb and mixed it into her tea. It tasted so awful that she couldn't bring herself to drink it. She solved the problem by encapsulating the drug with a manual pill filler and taking it along with her prescribed medication.

"Literally a couple of days after I started taking it, the bleeding stopped," she said. "All my symptoms went away." Things went so well that she tapered off all the other medications and even forgot to take her herbal remedy on vacation. After a couple weeks, her symptoms flared up again. When she went back on her pills, the symptoms receded, convincing her of their effectiveness.

In the age of social media, many of us would have dashed off an enthusiastic Facebook post to a support group to spread the word. But that approach never occurred to Saiki. She wanted doctors to be able to prescribe this as a drug, and for patients to be able to pick it up at their pharmacy. "I wanted to do this the right way," she explained. "I wanted to develop a new treatment for ulcerative colitis patients." (Because she is seeking to have the drug commercially licensed, Saiki asked that the drug's source not be identified in this article.)

A musician among the scientists

Saiki's first inquiries about legitimizing the treatment were to her chamber group's cellist, who — this being Stanford — was also a doctor and professor of hematology. He recommended a literature search. Combing through the scientific publications, she found that no one had performed a clinical trial.

Saiki also typed "drug development" into Stanford's online course catalog. "CSB 240A — A Practical Approach to Drug Discovery and Development" came up. She emailed the instructors — associate professor Kevin Grimes, MD, and professor Daria Mochly-Rosen, PhD, both in the Department of Chemical and Systems Biology — asking to enroll.

They turned her down.

She didn't have the scientific background, they explained. Because the class was group-project-based, if Saiki couldn't keep up, it would hurt her classmates, as well.

But Saiki refused to give up. She believed in her remedy and its usefulness to others. "The class was exactly tailored to what I wanted to learn. It's the only class really available on the topic," she said.

"She kept saying, 'Just give me a chance — I can study, I can learn,'" recalled Mochly-Rosen, who is also the George D. Smith Professor in Translational Medicine. "She's a very unassuming person; you don't expect she'd be so insistent."

In the winter quarter of 2011, Mochly-Rosen let Saiki enroll, despite concern that she wouldn't be able to keep up.

Saiki, Mochly-Rosen observed, was a quiet student, but whenever she was directly questioned about her group's progress or approach, her answers were clear and confident. Saiki admits that initially the science lectures were over her head, but her group's project — a probiotic treatment for *Clostridium difficile* infections — included market research and how to satisfy regulatory requirements, things Saiki found she could contribute to. She set about to master the individual parts of the process, similar to how she would approach a new piece of music. "You pick things up once you start putting the pieces together," she said.

Privately, she'd replicate each assignment for her own drug. When Saiki showed the results to her instructors, they invited her to present her work to the class.

On the final day of class, after the groups had presented, Saiki pitched the remedy as a potential drug to treat ulcerative colitis. She began with side-by-side medical colonoscopy photographs. The image on the left was puffy, angry-red and inflamed. The one on the right was smooth with faint blood vessels crisscrossing healthy pink tissue. This, Saiki explained, was her colon before and after she began treating herself. From there she carefully laid out the development and regulatory steps needed to bring the drug to clinical trial. After her presentation, Mochly-Rosen, Grimes and the industry guest who was helping to evaluate the students agreed that Saiki should present to the SPARK group.

SPARK was started in 2006 by Mochly-Rosen to support Stanford scientists and doctors in transforming promising compounds into clinical drugs. Every year, a dozen projects, out of nearly 200 considered, are selected for funding and advising support. Successful candidates range from graduate students to professors with full labs. Saiki wasn't aware she was auditioning; she was just excited for the chance to get feedback.

NORBERT VON DER GROEBEN

Saiki was a graduate student in musicology at Stanford before switching to the PhD program in chemical and systems biology.

'Like a performance'

On the day of her presentation, Saiki calmly addressed the gathered Stanford faculty and industry professionals. Saiki may have been playing catch-up with many aspects of the world of science, but when it came to taking the stage, she had a long history.

"Most musicians have a journey with nerves," explained Saiki's former violin instructor, Laura Klugherz, a music professor at Colgate University and director of the Colgate Chamber Players. With each recital, each solo performance, more of their nervousness rubs away until the fear is gone. "Julie traveled that journey diligently and successfully," Klugherz said.

"Her presentation was bam!" said Lyn Frumkin, MD, PhD, a SPARK adviser, recalling the first time he heard Saiki present at a meeting about her projects status. "From the time she opened her mouth to the time she finished — clear, articulate, interesting, like a performance."

It wasn't just the delivery. Frumkin was impressed by the originality of Saiki's idea and her deep understanding of the scientific and bureaucratic steps required to establish her drug's efficacy. He was stunned when he learned that Saiki's background was in music.

Other members of the SPARK advisory board were similarly won over. They invited Saiki to join SPARK, and in 2011 awarded her a $50,000 Spectrum pilot grant, supported through a Clinical and Translational Science Award from the National Institutes of Health, to develop SA100, the working name for her drug. Since then, she's gone on to raise other sources of funding for her project.

Now she had to obtain permission from the FDA through its investigational new drug application. Frumkin, who's worked in the drug industry for more than 20 years, described producing an IND application as "a lengthy process, analogous to a term paper a thousandfold." Beyond making a scientific and medical case for the drug, the IND application must justify drug dosages, manufacturing decisions and clinical study designs, explain how the results will be assessed, and address statistical, regulatory and quality-assurance issues.

"Few, except people in industry, really write them," said Frumkin. He and Saiki pored over her initial first draft and as well as successful IND applications. For each section, Saiki asked detailed questions. "She wanted to know the reason things were one way versus another," said Frumkin.

Outside of SPARK, Saiki was getting up to speed on the science and business of drug development. She earned a master's degree in medicine from Stanford in the spring of 2014, a program that teaches a medical school curriculum without the clinical courses and is designed to prepare science and engineering graduate students for medical research. And in the summer of 2013 she interned at Genentech, a Bay Area drug company.

Drawing on this new knowledge, Saiki and her team wrote their nearly 400 page IND application and sent it off to the FDA. It was accepted in 2014. SA100's effectiveness would be confirmed, or denied, by a clinical study.

Into the clinic

Unlike large drug companies that can access multiple centers across the United States to run clinical trials, Saiki and the doctor running the trial, Shamita Shah, MD, until recently a Stanford clinical assistant professor of gastroenterology and hepatology, could recruit only patients within driving distance of Stanford. And they were looking for a particular type of patient, one who wasn't responding to the initial 5-aminosalicyic acid treatment but had not yet moved to immunosuppressive drugs — the stage that Saiki was in when she began using her homemade pills.

The similarity wasn't intentional — this was the best group on which to test both the safety and efficacy of SA100 — but Saiki admits to an emotional connection to these patients' predicament.

"We felt the patient group in greatest need was the one that failed 5-aminosalicyic acid treatment," she said. "For that reason, we wanted to go straight to those patients and see if it works."

That type of patient has proved difficult to find. While Shah, who was the clinical director of Stanford's inflammatory bowel disease program, had numerous patients with ulcerative colitis, most had advanced cases and had already switched to immunosuppressants or other treatments. Saiki and Shah reached out to local clinics but found no eligible patients.

Undaunted, they've expanded their search to social media and patient support groups to find patients to enroll. And Shah's recent relocation to the Ochsner Health Center, in New Orleans, means they can look for participants in two locations. Shah is excited to continue her collaboration with Saiki. "She's been the passion behind the study," Shah said. They hope to enroll the 24 patients needed for the trial within the next year.

While Saiki was achieving success with SPARK and her science classes, she was struggling with her musicology PhD. Her interest in medicine drew her away from her research on chamber music. She tried to merge the two by looking for relationships between music and medicine but found that the ways she approached these subjects were too different. She said, "it was very hard to even have an interesting conversation" between them, much less a thesis.

SA100's development was demanding much of her time, and new medical research opportunities were coming her way. She had to make a choice.

"For so many years, I've worked toward this path. Everything — practicing long hours, learning German, spending time abroad — all that was in preparation for an academic career in music," she said. "Withdrawing was truly hard because I felt like I was just giving up."

But medical research, specifically drug development and other interventions to improve patient health, excite her more, she said. She hasn't turned her back on music, but now she more frequently wields a pipette than a violin bow.

"I feel like I am working on something that can potentially help someone," she said. "At the end of the day, that experience is very gratifying."

Those interested in learning more about Saiki and Shah's ulcerative colitis clinical trial can contact clinical research coordinator Ankita Dubey at ankita.dubey@stanford.edu. **ISM**

Kim Smuga-Otto is a former science-writing intern for the medical school's Office of Communication & Public Affairs.

Recovery

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healthy recoveries have not.

"Some people feel great after a few days, some are in bed for a month and we don't know why," said Gabriela Fragiadakis, a graduate student in microbiology and immunology. Fragiadakis shares lead authorship of the study, which was published online Nov. 17 in *Anesthesiology*, with Brice Gaudilliere, MD, PhD, clinical instructor of anesthesiology, perioperative and pain medicine. The senior authors are Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine, and Garry Nolan, PhD, professor of microbiology and immunology. The study will also appear in the December issue of the journal.

Focusing on monocytes

Gabriela Fragiadakis

The researchers discovered that the behavior of monocytes, the largest type of white blood cells, in patients before surgery was linked to the length of their recoveries. As much as 50 percent of the variation in a patient's recovery time could be predicted based on these cells' behavior. Previously studied predictors, such as the patients' mental states or the number of immune cells at the wound site, generally account for at most 10 percent of the variation seen in patients' recovery times.

Knowing the likely recuperation times will help patients plan better for their return to work and other post-surgery commitments. For patients at risk for longer recovery times, doctors could schedule additional physical therapy or special care, or the surgery could be postponed while exercise, dietary changes and stress-release techniques are implemented.

The work expands on research published last year on 32 patients recovering from hip-replacement surgery. These patients were relatively healthy and had complication-free surgeries. The researchers found a strong link between the speed at which these patients regained hip strength and mobility and how monocytes functioned in their blood shortly after surgery. While the cells were active in all cases, patients with supercharged monocytes took weeks longer to regain abilities such as getting out of bed, standing or walking.

Monocytes are some of the immune system's first responders. They sense the distress call from damaged cells, be it from an invading pathogen or the clean cut of a surgeon's knife. When the monocytes arrive on the scene, they go to work clearing away cellular debris and initiating wound healing. But a bigger early response of monocytes in the blood isn't necessarily better. It may disrupt the cells' ability to sense the location of the wound and slow down the healing process, said Angst.

'Surgery' in a test tube

In previous work by the researchers, the overactive monocytes and their relationship to patient recovery were measurable one hour after surgery. The next question, addressed in the current study, was whether these patterns in monocytes could be detected before a patient was wheeled into the operating room.

The researchers simulated surgery conditions in a test tube using blood they had collected from 25 of the patients in the original study an hour before the surgery. Gaudilliere likened this approach to a cardiac stress test, in which the heart is forced to work harder by having patients run on a treadmill to uncover underlying health issues. For this "immune stress test," the researchers mixed known signaling molecules into the blood samples to trigger specific responses from the immune cellular machinery, similar to what might be set in motion during surgery.

Martin Angst

They then analyzed the cells using mass cytometry, a technique developed in the Nolan lab that sorts and characterizes cells based on chemical tags. The tags not only precisely identify the cell types, but also reveal the internal, cell-specific processes that control the cell's behavior. Supporting their previous observations, they found that the speed at which patients regained hip function was related to the cellular processes of the monocytes.

Brice Gaudilliere

By detecting signals from injured tissue, monocytes play a critical role in wound healing by forming new connective tissue and blood vessels. Angst suspects that when the monocytes are overly activated by surgery, their ability to migrate to the incision site is impaired.

To see if an exaggerated response by monocytes delays healing, Angst and Gaudilliere are now using imaging technology to observe the cells in the wounds of patients undergoing surgery, as well as in wounds of mice who undergo a surgery that is similar to the hip replacement studied in patients.

Replicating the study

Dan Sessler, MD, professor and chair of outcome research at the Cleveland Clinic, who was not involved with the study, sees great value in adapting the paper's results into a test. Predicting a patient's recovery is "clinically important, and we don't do a good job," he said.

In a new Stanford study with a larger cohort — about 80 hip-replacement patients — Angst and Gaudilliere are hoping to refine the initial study's findings. They will assign more of the mass cytometer's chemical tags to the cellular machinery of the monocytes, allowing them to closely study the cells' internal processes and increase their understanding of cellular events that best predict recovery after surgery.

"The first study was exploratory," said Angst. "We are now in the position to ask specific questions and prospectively validate our findings." If his team can pinpoint the most critical activated proteins, they can develop a simpler assay. Most hospital labs already have cell analysis machines that could readily measure activity of the monocytes. "Once we know what we're testing for, we can use simpler methods using machines already in the hospital, and it can be done in a couple of hours," said Fragiadakis.

The development of a surgery-recovery prediction test is an example of Stanford Medicine's focus on precision health, which aims to enable researchers and physicians to better predict individual risks for specific diseases, develop approaches to early detection and prevention, and help clinicians make real-time decisions about the best way to care for patients.

Other Stanford-affiliated co-authors on the paper are research associate Edward Ganio, PhD; research nurse Martha Tingle; and postdoctoral scholar Nima Aghaeepour, PhD.

The study was supported by Stanford Bio-X, the Ovarian Cancer Research Fund, the Canadian Institute of Health, the International Society for Advancement of Cytometry, the Baylor Research Institute, Northrop Grumman Corp., the California Institute for Regenerative Medicine, the European Commission, the Food and Drug Administration, the Bill and Melinda Gates Foundation, the Alliance for Lupus Research, the Lymphoma Research Foundation, the U.S. Department of Defense, the Entertainment Industry Foundation and the National Institutes of Health.

Nolan holds a patent on the mass cytometry technology, which is manufactured by Fluidigm. He also holds Fluidigm equity. Stanford holds a provisional patent on a blood diagnostic test based on the research.

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

ISM

Kim Smuga-Otto is a former science-writing intern for the medical school's Office of Communication & Public Affairs.

Depression

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even with adequate insulin production in the pancreas — and mood disorders."

Insulin is released by the pancreas in response to food intake. It alerts cells throughout the body to the presence in the blood of glucose, the body's primary energy source. The cells of people with insulin resistance fail to take up glucose adequately, eventually resulting in high blood levels of the sugar, which is deleterious to multiple tissues in the body.

Insulin resistance — a precursor to Type 2 diabetes — and major depression are common conditions. Close to one in five Americans are diagnosed with depressive illness at some point in their lives, Rasgon said, while about one in three otherwise healthy Americans — and an even greater share of people with depression — are insulin-resistant.

"While insulin resistance is more prevalent among people who are overweight or obese, significant numbers of people with normal weight are insulin-resistant, too," she said. "But most don't find out about it until they're diagnosed with Type 2 diabetes, hypertension or cardiovascular disease."

Insulin resistance is associated with higher likelihoods of many chronic diseases, among them Alzheimer's disease and depression.

Mirroring earlier results

The insulin-sensitizing drug pioglitazone is approved by the U.S. Food and Drug Administration for treatment of Type 2 diabetes. Marketed for many years under the trade name Actos, it is now available generically. In a pilot study published in 2010, Rasgon and her associates found that administering a similar drug, rosiglitazone, to depressed patients who were insulin-resistant alleviated their depression. However, no placebo was used, and both the researchers and participants knew which treatment was being administered.

"I wanted to replicate that study's findings in a controlled experimental design," Rasgon said. The new trial was placebo-controlled, and researchers were blinded as to which patients were receiving pioglitazone versus a placebo. The patients didn't know which they were getting, either. Furthermore, not only insulin-resistant but also insulin-sensitive patients, all between the ages of 23 and 71, participated.

All the patients had been experiencing episodes of depression lasting, on average, more than one year. Their symptoms had failed to remit under standard treatment regimens. They remained on these regimens for the duration of the Stanford study and, in addition, were given either pioglitazone or a placebo.

The patients were tested for depression severity and insulin resistance at the study's outset and then roughly every two weeks from the beginning of the trial to the end. A total of 37 patients — 29 women and eight men — completed the study.

The insulin-sensitive subjects showed a decline in severity of depression regardless of whether they received pioglitazone or a placebo, the researchers found, and the difference in the degree of those two groups' improvement was statistically insignificant.

But among the insulin-resistant group, those given pioglitazone showed a much greater improvement than those who got a placebo. They also showed more improvement than insulin-sensitive patients did.

"The people who didn't get better are the people who are insulin-resistant and didn't get pioglitazone," said Kathleen Lin, a graduate student in Rasgon's group who shared lead authorship with Tonita Wroolie, PhD, clinical associate professor of psychiatry and behavioral sciences.

The more insulin-resistant a participant was at the beginning of the study, the better the drug's antidepressant effect, the researchers said. In addition, insulin sensitivity improved in insulin-resistant patients treated with pioglitazone — not a surprising result, given that the drug was designed for that purpose.

Equally intriguing is what did not happen. Unlike members of the control group, insulin-resistant patients' depression was not relieved by the placebo. This suggests, Rasgon and Lin said, that whatever it is that allows insulin-sensitive patients' depression symptoms to diminish over time doesn't seem to work for insulin-resistant patients. It could be, they speculated, that for some patients, insulin resistance is a barrier to the effectiveness of standard antidepressant therapies, which may kick into gear only once the patients' insulin resistance is reduced.

Rasgon cautioned that the study was small and short-term and needs to be replicated on a large-scale, longer-term basis. But, she said, insulin's importance in brain function is well-documented. The brain, in fact, is a glucose glutton, accounting for one-fifth of all glucose consumption in an active human being. So it stands to reason that impaired glucose uptake due to insulin resistance would affect many pivotal processes in the brain, including regulation of emotion and cognition, and that the effect could become detrimental.

The research reflects 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.

"There's enough evidence now to say that insulin-sensitizing drugs may have a place in treating chronic mood disorders in insulin-resistant subjects," Rasgon said.

"This finding may help us to determine which therapies are best for which person," said Lin. "We're trying to get a little better at that."

Thalia Robakis, MD, PhD, clinical assistant professor of psychiatry and behavioral sciences at Stanford, also contributed to the study.

The study was funded by a grant from the National Institutes of Health.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. ISM

Using Apple HealthKit to care for patients with Type 1 diabetes

By Stacy Finz

Lori Atkins' 16-year-old son, Blake, has Type 1 diabetes, and she used to track his blood-sugar readings by hand.

It was time-intensive and sometimes daunting, like the night he had a cold and "his numbers were going crazy." Lori paged Blake's doctor and sat at a computer, where she wrote a detailed email listing her son's glucose measurements over the preceding 12 hours to ensure the physician had all the vital data.

Now, however, Blake's glucose readings are available at his doctor's fingertips.

Rajiv Kumar, MD, a pediatric endocrinologist at Stanford Children's Health and Lucile Packard Children's Hospital Stanford, can access the teenager's blood-sugar readings quickly, without his mom having to crunch numbers or schedule a clinic appointment. And it's all because of a new health-care platform from Apple.

In September 2014, the company released Apple HealthKit, a technology that can securely share patient-generated data with third-party applications, including Epic MyChart, the electronic medical record and patient portal system used by Stanford Children's Health.

Pilot program

Kumar began piloting HealthKit in March with 10 patients, including Blake, to assess its ability to track blood-sugar levels. Kumar is so pleased with the results that he is now planning to offer the program to more of his patients who use a continuous glucose monitor.

"We're very excited about this experience," he said. "Our endocrinologists are now able to easily assess large volumes of blood-sugar data between clinic visits — and quickly identify trends that could benefit from insulin dosing regimen changes."

"There is also an added benefit," said Kumar, who is a clinical assistant professor of pediatric endocrinology and diabetes at the School of Medicine. "We no longer need to download the data during clinic visits, and this allows us to spend more time with our patients and their parents."

How does it work? Patients like Blake wear a continuous glucose monitor that sends 288 blood-sugar readings a day to an Apple mobile device through Bluetooth. The data is securely transmitted via HealthKit into the patient's electronic medical record at Stanford Children's Health through the MyChart app.

The work is an example of Stanford Medicine's focus on precision health, the aim of which is to generate care that is proactive, predictive and personalized.

Blake was diagnosed with diabetes four years ago, and he said that using a monitor linked to his iPhone has been a game changer.

In the past, he and his mother tried to be diligent about communicating his glucose measurements and assessing insulin dose needs — a necessity for treating the disease. But this wasn't easy for Blake, who has school, homework, soccer practice and myriad activities that keep him busy. That left most of the onus on Lori.

'It's taken the pressure off'

Now, if she or Blake has questions or concerns about trends in his glucose readings, they can simply send a message to Kumar through MyChart. Blake's recent glucose readings will have been automatically uploaded to his electronic medical record and ready for Kumar to examine. "I love it," said Lori.

And for Blake, no additional effort is required.

"It's not a hassle at all," he said, adding that other than changing out the filament sensor for his continuous glucose monitor once a week, he doesn't have to track anything because HealthKit does it for him. "It's taken the pressure off."

NORBERT VON DER GROEBEN

Rajiv Kumar, a pediatric endocrinologist, can track Blake Atkins' blood-sugar readings with the help of technology that transmits the information to the teen's electronic medical record.

Having easy and timely access to Blake's cumulative data helps Kumar see the big picture. "By being able to look at a block of time, I'm able to detect patterns and pinpoint trends," said Kumar, who sees patients at Lucile Packard Children's Hospital and other Stanford Children's Health locations, including California Pacific Medical Center in San Francisco and John Muir Health in Walnut Creek, California. "I'm also learning more than I would from a routine, three-month patient visit. It's just a much more streamlined system." **ISM**

Stacy Finz is a freelance writer.

OF NOTE

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

LINDA BOXER, MD, PhD, vice dean of the School of Medicine, was awarded the J.E. Wallace Sterling Lifetime Achievement Award in Medicine by the Stanford Medicine Alumni Association. She earned a medical degree and doctorate from the School of Medicine. She is the Stanley McCormick Memorial Professor, a professor of medicine and chief of hematology. Her research focuses on hematologic malignancies.

EDWARD DIAZ, MD, was appointed assistant professor of urology, effective Sept. 1. He specializes in the use of robotic surgery in pediatric urology. His most recent project examines how genetically engineered mesenchymal stem cells can promote bladder tissue regeneration.

RAMI EL ASSAL, DDS, postdoctoral scholar in radiology, was named a fellow of the Academy of Dentistry International, an honor for distinguished dentists worldwide. His research focuses on the use of nanotechnology and bio-inspired materials in regenerative and transplantation medicine.

SUSAN HINTZ, MD, professor of pediatrics, was appointed co-director of the Johnson Center for Pregnancy and Newborn Services at Lucile Packard Children's Hospital Stanford and Stanford Children's Health. She will continue to serve as the medical director of the Fetal and Pregnancy Health Program. She holds the Robert L. Hess Family Professorship. Her research focuses on neurodevelopment in premature and high-risk infants.

TANYA STOYANOVA, PhD, was appointed assistant professor of radiology, effective Nov. 1. Her research focuses on the molecular mechanisms underlying cancer development. In particular, she studies signaling cascades initiated by cell surface receptors that are involved in prostate cancer initiation and progression.

DEAN WINSLOW, MD, was appointed professor of medicine, effective Sept. 1. As academic physician-in-chief at Stanford Health Care-ValleyCare and vice chair of the Department of Medicine, he will develop clinical, teaching and research programs at Stanford's community health care system in the East Bay. He also focuses on bedside medicine and mentoring students, residents and junior faculty. **ISM**

Linda Boxer

Edward Diaz

Rami El Assal

Susan Hintz

Tanya Stoyanova

Dean Winslow

Vaccination exemptions in California cluster in white, affluent communities

By Becky Bach

California's recent measles epidemic was no fluke: Between 2007 and 2013, the percentage of the state's kindergarteners using a "personal belief" exemption to enroll in school without vaccinations doubled.

In the 2013-14 school year, 3 percent of California kindergarteners entered school unvaccinated. In some schools, the percentage of vaccinated children was so low that it threatened herd immunity, or the ability for a population to keep a pathogen at bay, according to Michelle Mello, PhD, JD, a Stanford professor of law and of health research and policy.

To understand the rapid increase, Mello worked with a team led by Tony Yang, ScD, at George Mason University. Their research was published Nov. 12 in the American Journal of Public Health.

They found the highest resistance to vaccinations among white, affluent communities. In contrast to previous studies, however, they did not find a correlation between higher levels of education and vaccine exemptions.

"Beliefs about vaccination risk tend to be more entrenched among certain communities of mothers," Mello said. The study didn't investigate reasons for seeking exemption, but other studies suggest some mothers in affluent communities may believe they can adequately protect their children through "intensive parenting techniques" such as an organic diet and restricting contact with sick children, she said.

> "Beliefs about vaccination risk tend to be more entrenched among certain communities of mothers."

Although California eliminated the personal belief exemption this summer in a broad-reaching law that requires all medically eligible children who attend a public or private school or day care to be vaccinated, the study speaks to how other states might approach the problem of vaccine exemptions, Mello said.

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California eliminated the personal belief exemption with a law that requires vaccinations for medically eligible children who attend a school or day care.

Similar clusters of vaccine resistance exist elsewhere, and the findings could help public health agencies refine outreach methods, she said. For example, by specifically targeting local groups and reaching out to community leaders, officials may have more success providing education about vaccine risks and benefits, Mello said.

The results are particularly striking given the history of vaccination efforts, she said. In the first half of the 20th century, public health officials struggled to ensure vaccines reached disadvantaged communities. Now, as fear of the targeted diseases has paled, parents may be more fearful of vaccines, leaving the entire population vulnerable. **ISM**