

S T A N F O R D
M E D I C I N E

Summer 2018

special report

THE FUTURE

HUMAN CENTERED,
DISCOVERY LED

Forward thinking

Value focused, digitally driven,
uniquely Stanford

AI with heart

How artificial intelligence
can bring more humanity to health care

Sparking

From the ivory tower to the patient

Keep bugging me

Microbes as healers

Around the globe

Delivering high-tech,
high-touch health

Realizing precision health

A new center aims
to stop disease in its tracks

plus

At wit's end

A diagnostic mystery solved

Team effort

Data galore from
one professor's lung tissue



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MICROFACTORIES

RESEARCHERS ENGINEER BREWER'S YEAST TO PRODUCE A COMPLEX DRUG THAT'S IN SHORT SUPPLY

Christina Smolke, PhD, says it took a lot of finesse to successfully engineer yeast so it can pump out sizable amounts of a cough suppressant that is found naturally in opium poppies and has potential anti-cancer properties. "It's as if we're grabbing a couple dozen soldiers from different units, deploying them on Mars and telling each of them, 'Now, not only am I putting you on Mars, but I want you to get some serious work done here, and I want you to work with these other soldiers you haven't worked with before — many of them total strangers,'" said Smolke, professor of bioengineering at Stanford. "Good luck with that."

But, through ingenuity and new technology, researchers in Smolke's lab figured out how to get cells of brewer's yeast to make the complex compound, called noscapine.

Though noscapine is normally extracted from opium poppies, it is non-narcotic. Its medicinal value for suppressing coughs was discovered in 1930, and since the 1960s it has been used for that purpose around the world, including in much of Asia, Europe and South America. More recently, the drug has been studied in mice for potential as a cancer drug — scientists believe it is less toxic to healthy cells than current chemotherapy treatments.

Tons of noscapine are extracted annually from opium poppies that are mostly grown in Australia, but also in India, France, Turkey and Hungary. The cost is high and supply can be inconsistent, a result of strict opium crop regulations, a slow growing period — it takes a year for plants to mature — and the crop's vulnerability to such environmental conditions as pests, bad weather and varying nutritional characteristics of the soil where it's grown.

Bioengineered yeast from Smolke's group, however, can inexpensively manufacture large amounts of noscapine in three or four days. Researchers succeeded by inserting 25 foreign genes — many from poppies, but several from other plants and rats — into a single strain of brewer's yeast. All of those genes were recipes for enzymes — protein machines that, working together, can build complex substances from simple starting materials.

Using CRISPR, a gene-editing tool, the researchers altered some of the plant, rat and yeast genes, and the medium in which the yeast multiplies, to help everything work better together.

In other words, Smolke said, "We modified them to keep them in shape on this planet and to get along with one another better, and we nudged the yeast to help these enzymes grab the resources they need to get the job done."

The result was an 18,000-fold improvement in noscapine output when compared with what could be obtained by just inserting the plant and rat genes into yeast. "This is a technology that's going to change the way we manufacture essential medicines," Smolke said.

An additional hundredfold improvement will be necessary for commercial viability, but much of that can be achieved by substituting large-scale bioreactors for simple laboratory flasks, she said.

"We're no longer limited to what nature can make," Smolke said. "We're moving to an age where we can borrow nature's medicine-manufacturing processes and, using genetic engineering, build miniature living factories that make what we want."

A paper describing the research was published online April 2 in the *Proceedings of the National Academy of Sciences*. Smolke is the senior author. Stanford's Office of Technology Licensing holds pending patents on intellectual property associated with the findings in the study. — BRUCE GOLDMAN



Under Christina Smolke's direction, researchers bioengineered yeast to produce sizable amounts of a cough suppressant found in poppies that also has promise for treating cancer.

S T A N F O R D M E D I C I N E

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Human centered, discovery led



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letter from the dean

I appreciate the old witticism that it's hazardous to make predictions about the future, but as scientists and physicians, wondering how to make life better is in our DNA.

Every day, researchers ask questions that transform the impossible into the possible. Physicians work with each and every patient to ensure a healthier future. And as the dean of our academic medical center, my life's work is to peer into the fog and try to position us to do the most good not just next year but in the next decade and beyond.

It's in this same spirit that we devote this issue of the magazine to the future — specifically, the future of Stanford Medicine. But I don't think I overstate the case to say that the future of Stanford Medicine will also, in many ways, be the future of medicine itself. After reading the stories, I think you'll agree.



Three years ago, Stanford Medicine established our precision health vision. Maximizing the potential of digital health and biomedical advances, precision health will predict and prevent disease before it strikes, cure it definitively when it does and do it all precisely.

We set out to lead that revolution and the decision has energized Stanford Medicine.

A year ago, we came together again to ask how the School of Medicine, Stanford Health Care and Lucile Packard Children's Hospital Stanford could better collaborate to achieve our inspiring vision. The resulting integrated strategic plan was an institution-wide effort that created the framework we'll use to leverage our combined creative might to remain on the forefront of the precision health revolution.

In this issue, you can read about this process and how Stanford Medicine is alive with innovative teaching, science and health care that is bringing the precision health future into focus today. You'll also see how a palliative care physician uses a Stanford-born computer program to identify the patients who most need her attention, showing that even at the end of life, precision health efforts can lead to better patient care. Another story highlights how interdisciplinary research by bioengineering, pathology and microbiology colleagues may one day generate stable, resilient microbiota that prevent or mitigate cardiovascular disease and inflammatory bowel disease.

Of course, our precision health efforts are not limited to our campus. As we discovered during the strategic planning process, the Stanford community takes our global responsibilities to heart. You'll read about how this commitment manifests itself as unique efforts to improve ambulance service in Nepal, contain hepatitis B in China and as programs that export the very processes of discovery and translational research. It is imperative that the precision health revolution be enjoyed worldwide.

Imagining a brighter future where people live longer and healthier lives is what Stanford Medicine is all about. Read on to learn more about how we're creating that better future today.

Sincerely,

Lloyd Minor, MD

Carl and Elizabeth Naumann Dean of the School of Medicine

Professor of Otolaryngology-Head & Neck Surgery

GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Coral decoded

RESEARCHERS HAVE FOUND that CRISPR gene-editing technology could be effective for analyzing the genetic makeup of coral and the role genes play in the animal's survival and establishment of new colonies.

"Up until now, there hasn't been a way to ask whether a gene whose expression correlates with coral survival actually plays a causative role," said coral geneticist Phillip Cleves, PhD, a post-doctoral scholar at Stanford, who led a study testing the feasibility of using the gene-editing system to understand coral biology. "There's been no method to modify genes in coral and then ask what the consequences are."

In the late 1990s, the ocean's coral reefs experienced the first big wave of coral bleaching, in which ocean conditions — most prominently increasing temperatures — kill off or bleach coral. It turned the once-vibrant colors bland and damaged the entire reef ecosystem.

To better understand how coral pro-



duces the colors, and to aid in coral conservation, researchers used the CRISPR gene-editing system to make tweaks that knocked out the genes responsible for certain colors and for regulating colonization.

"If we can start classifying which genes are important, then we can get an idea of what we can do to help conservation, or even just to predict what's going to happen in the future," said Cleves, lead author of the study, published April 23 in the *Proceedings of the National Academy of Sciences*.

Exposure to pollutants in sub-Saharan Africa led to 400,000 otherwise preventable infant deaths in 2015, a Stanford study said. Visit <https://stanford/2tS5JN8>

Spotting autism

LOW LEVELS OF THE HORMONE vasopressin in fluid around the brain could be an autism biomarker. Researchers made the discovery by testing cerebrospinal fluid collected from autistic children and from monkeys with low sociability.

Stanford and UC-Davis scientists led the research, described in a paper published May 2 in *Science Translational Medicine*.

Autistic children are diagnosed over time through parent feedback and clinical observations. A biological test could speed diagnosis and treatment, said lead author Karen Parker, PhD, associate professor of psychiatry and behavioral sciences.

Aging stem cells revived

CLUMPS OF PROTEIN associated with such neurodegenerative diseases as Alzheimer's are present in stem cells in young mouse brains, a finding that could help Stanford scientists figure out how to reboot aging neural stem cells to maintain brain health.

The clumps, called aggregates, form when damaged or diseased proteins in neural stem cells bunch together. They collect in cellular trash bins known as lysosomes, which "digest" and eliminate them. As cells age, however, they are less able to dispose of aggregates, which impedes their ability to make new neurons.

Anne Brunet, PhD, professor of genetics and senior author of a paper describing the research published March 15 in *Science*, said researchers were surprised by the finding because

resting young cells were understood to be "a really pristine cell type just waiting for activation."

"But now we've learned that they have more protein aggregates than activated stem cells, and that these aggregates continue to accumulate as the cells age," she said. "If we remove these aggregates, we can improve the cells' ability to activate and make new neurons," bringing aging neural stem cells "back to life," and, perhaps, turning back the clock on such aging effects as memory loss and difficulty discerning smells.

FIGHT, FLIGHT OR FREEZE

WHEN YOU FEEL THREATENED, do you hide, freeze or stand your ground?

It turns out that two small clusters of adjacent nerve cells in your brain are responsible for your reactions and could be manipulated to change them. While exposing mice to perceived overhead threats, Stanford scientists were able to elicit timid or bold behavior in response to the threat by targeting and stimulating the two nerve cell clusters.

"This opens the door to future work on how to shift us from paralysis and fear to being able to confront challenges in ways that make our lives better," said Andrew Huberman, PhD, associate professor of neurobiology and of ophthalmology and senior author of a paper describing the research, published online May 2 in *Nature*.

Heart disease end run

EVEN PEOPLE WHO ARE genetically prone to heart disease can improve their heart health by being more active, one of the largest observational studies on fitness and heart disease found.

The Stanford-led study examined data collected from nearly a half-million people in the UK Biobank database.

Researchers found that people with higher levels of fitness and physical activity have lower levels of such negative health outcomes as coronary artery disease, stroke and atrial fibrillation, regardless of their level for genetic risk of heart disease.

For example, high-risk people who also have high levels of cardio-respiratory fitness have a 49 percent lower risk for coronary heart disease and a 60 percent lower risk for atrial fibrillation compared with study participants with low cardiorespiratory fitness.

Because little has been known about the risk-modifying effects of exercise in people with increased genetic risk of cardiovascular disease, these results could have significant ramifications for public health, the study said.

"This is important because of how we advise our patients," said study senior author Erik Ingelsson, MD, PhD, professor of cardiovascular medicine. "It's basically indicating that you can make some lifestyle changes, be more physically active and it can make a difference to your long-term health."

A paper describing the research was published April 9 in *Circulation*.



A welcome breath

MORE THAN 20,000 INFANTS in the United States are born so early every year that they can't make enough surfactant, a substance that keeps the tiny air sacs in their lungs open. Without it, they can't breathe.

People who have lung damage from severe infections, car accidents or near-drownings experience the same problem because surfactant leaks out when lungs collapse from trauma.

One way to keep these people breathing is to provide additional surfactant, which reduces the amount of force needed to inhale by lowering the tension of the inner surface of the lungs. Synthetic options are available, but the more effective natural replacement comes from the lungs of cattle or pigs, which is cost-prohibitive, especially in developing countries. "You get only a tiny amount per animal," said Annelise Barron, PhD, associate professor of bioengineering. "And whatever you've collected, you have to purify very carefully, as the material is so fragile you can't treat it with high heat to kill microbial pathogens."

Barron has bioengineered stable, synthetic substitutes that mimic the two special proteins — surfactant proteins B and C — that make surfactant effective. She hopes they can be tested soon in a clinical trial of adults in intensive care units who might benefit from surfactant replacement.

A paper about the research, published May 1 in *Scientific Reports*, said researchers found the material to be more effective at restoring breathing capacity in rats with damaged lungs than animal or synthetic surfactant, for about half the cost.

"It would, finally, be available to premature babies in developing countries like Bolivia, where my father was born," said Barron, co-senior author of the paper.

BEYOND BRCA

IN RECENT YEARS, more women with breast cancer have been undergoing tests to detect multiple gene mutations rather than tests uncovering only BRCA gene mutations, a study at Stanford and five other institutions showed.

More than 5,000 women diagnosed with stage-0 to stage-2 breast cancer between 2013 and 2015 were surveyed for the study, and a third of them underwent testing for cancer-associated mutations. The proportion who had multigene panel testing rose from about 26 percent in 2013 to about 66 percent by mid-2015. The proportion of women having only the testing for BRCA gene mutations dropped from about 74 percent to about 34 percent, according to the study, published May 10 in *JAMA Oncology*.

Multigene testing can provide better information to patients. Lead author Allison Kurian, MD, associate professor of medicine and of health research and policy, encourages newly diagnosed women to talk to their doctors about genetic testing options.



Giving back

PAUL BERG, 92, IS a Nobel-Prize-winning scientist, advocate, mentor, fundraiser and philanthropist. Known for helping develop recombinant DNA — the gene-splicing technology that transformed genetic medicine and launched the biotechnology industry — Berg recently created an endowed professorship with his wife, Mildred.

Mark Krasnow, MD, PhD, a professor of biochemistry, is the inaugural holder of the Paul and Mildred Berg Endowed Professorship.

"Mark is a fine scientist and a gifted teacher. He has mapped the entire system of lung development. ... It's a remarkable achievement," said Berg, PhD, a founding member of Stanford's Department of Biochemistry.

'Mark is a fine scientist and a gifted teacher. He has mapped the entire system of lung development. ... It's a remarkable achievement.'

A SHARED VISION OF STANFORD MEDICINE'S FUTURE

stronger
together

BY JULIE GREICIUS

ILLUSTRATION BY MARK SMITH

Walking down the long, sunny first-floor corridor that connects Stanford Health Care to Lucile Packard Children's Hospital Stanford, Lloyd Minor, MD, the then-newly named dean of the School of Medicine, noticed something unusual. Along the ceiling, clustered in triplets about every 50 feet, were three sets of Wi-Fi routers.

Minor, who had arrived just months earlier in October 2012, soon learned that the School of Medicine, the adult hospital and the children's hospital each had its own, separate Wi-Fi system. It was, Minor thought, a metaphor for how siloed the three entities were. "I realized we had a lot of work to do," he said.

He wasn't the only one who sought a more cohesive environment. That organizational need was championed by faculty and staff, and led to an unprecedented milestone for Stanford Medicine's three entities: In January 2017, the three leaders of Stanford Medicine — Minor; David Entwistle, president and CEO of Stanford Health Care; and Christopher Dawes, then-president and CEO of Stanford Children's Health — kicked off a process to form an integrated strategic plan.

All academic medical centers engage in research, education and clinical care, and Stanford Medicine's leadership sought to braid these objectives together. The medical school and both health care organizations all embrace the mission to lead the biomedical revolution by bringing precision health to people around the world. Their leaders know that this will require collaboration between the researchers, educators and clinicians at their institutions as well as scholars across the university.

But without a framework for ongoing cooperation, their efforts would fall short.

Stanford Children's Health had already recognized the need for this type of framework in 2015, when it developed its own 10-year strategic plan to help guide the organization beyond the opening of the new Lucile Packard Children's Hospital Stanford. "It was a bold and achievable vision that also pulled in some of the related academic areas in both pediatrics and obstetrics," Minor said.

In 2016, Entwistle joined Stanford Health Care as the president and CEO. He was vocal in his enthusiasm for creating a joint plan, and his energy and vision galvanized the process.

"We have some of the brightest, most creative minds in the world right here at Stanford," said Entwistle. "What we needed was to organize and collaborate in a way that would enable us to not only adapt to a rapidly changing future, but to play a major role in shaping that future. It was exciting to join the organization just as it was fully harnessing its potential."

tOGETHER, THE THREE ORGANIZATIONS GOT DOWN TO BASICS: What are our shared values? And where do we want to be in 2025? Where are we today with regard to our aspirations? With those questions in mind, a diagnostic phase began. In January 2017, the integrated strategic planning team — led by Priya Singh, senior associate dean for the School of Medicine and chief strategy officer for Stanford Health Care, and Sean Hennessey, chief planning officer for the School of Medicine — sent a diagnostic survey to 16,000 individuals across the three organizations. By April, they had nearly 4,000 responses.

"During that phase, we wanted to find out: How do people feel? Do they even see a need for a strategy?" said Singh. "And we were thrilled that people really did. From the survey responses and from the one-on-one interviews we did, what we heard consistently was that the people at our organizations were hungry for strategic direction."

The survey responses were measured on a scale of 1 (lowest) to 5 (highest). The highest responses reflected enthusiasm from faculty and staff for Stanford Medicine's purpose,

which received an average score of 4.1, and its activities and roles, which scored 3.7. The lowest scores were in decision making, and in processes and systems/information technology, both at 3.1.

"We found that there was remarkable convergence and support for our mission, our vision and our values," said



Entwistle. "But there was a need for clarity — clarity about the relationship among the three entities, clarity about our priorities and clarity about how decisions were going to be made moving forward."

Singh, Hennessey and the team analyzed the survey results, sorted the responses into 13 subject areas, and created workgroups — each with two to four faculty or administrative co-leaders — to write in-depth reports on the challenges and opportunities in each area. Starting in August 2017, each group met at least twice a month, focusing on its area, such as digital health and innovation; promoting fundamental discovery; precision health; safety, quality and value; people, culture and community; and translational medicine.

The faculty workgroup for promoting fundamental discoveries, for example, reflected on Stanford's remarkable history of discovery in the basic sciences — from the biochemistry of DNA replication and repair in the 1960s, to research in the 1990s that led to complete genome sequencing and genetic treatments. "Although our foundations in basic science are strong, we can't take them for granted," said Suzanne Pfeffer, PhD, professor of biochemistry and co-leader of the workgroup. "We had to address several challenges for the coming years: decreasing federal support, increasing costs and competition for resources. Amid those challenges, we're drafting recommendations that will augment Stanford's existing vitality in research, support foundational discoveries in basic science that lead to cutting-edge clinical diagnostics and therapeutics, and enable new insights that can benefit the health worldwide."

Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology, saw the inherent value of capturing Stanford's worldwide influence in improving health. "Our key measure of impact lies in the discoveries we make right here at Stanford that go on to help people the world over and to move health care forward," Gambhir said. "Discovered here, used everywhere."

Enthusiasm for the process was building along the way, with new ideas emerging in the town hall meetings, open house events and retreats — attended by hundreds of stakeholders, and often hosted by Entwistle and Minor. Faculty and staff were essential participants, raising questions and issues and providing their input and influence. The collective effort to shape the future of Stanford Medicine — and of science and medicine itself — was catching on.

"What makes this such an exciting process is not only

are we trying to improve what we are now and how we take care of our patients now, but we're also trying to anticipate where medicine is going, and how we're going to be a high-value organization for patients in the future," said Dennis Lund, MD, interim president and CEO of Stanford Children's Health since Dawes' retirement in March 2018. "The way we deliver health care in 2025 is not going to be the way we deliver health care today. And so we're trying to anticipate that. Like the old Wayne Gretzky saying, we're trying to skate where the puck is going, not where the puck is."

fROM DECEMBER 2017 through January 2018, the strategy planning team analyzed the white papers from the workgroups and began to pull the themes together. "That's when the three big priorities emerged," said Hennessey, "and our set of potential initiatives for the strategy."

Those priorities — value focused, digitally driven, uniquely Stanford — now provide the heart of the plan, the basis for guiding future initiatives, tactics and decision-making for all three institutions.

"Finishing" the plan wasn't — and isn't — part of the plan, said Singh. "There is no such thing, we hope, as the 'final stage.' We absolutely do not want the strategic plan to be final in a way in which we can say, 'Oh, it's done,' and it sits on a bookshelf and starts to gather dust. We hope it will be a living, breathing guide to this organization on an ongoing basis."

What they have created is a roughly 2,000-word document enunciating the strategic priorities, goals and performance measures and outlining an annual planning process. This spring

Stanford Medicine's leadership shared the plan at a town hall meeting and with the university's board of trustees.

For Mary Leonard, MD, professor and chair of pediatrics and physician-in-chief of Lucile Packard Children's Hospital Stanford, the integrated strategy was "a very ambitious step," she said. "It addresses everything from promoting funda-

LOOKING AHEAD: David Entwistle, CEO of Stanford Health Care, left; Lloyd Minor, MD, dean of the School of Medicine, center; and Dennis Lund, MD, interim CEO of Stanford Children's Health.



mental discovery all the way to health care delivery models in this changing environment.”

In June, the plan was already in motion: Stanford Medicine announced the formation of a team working on digital health care integration for Stanford Health Care, which will first focus on telehealth and a virtual second-opinion program. A new leadership position was also created at the School of Medicine, associate dean of industry relations and digital health, to focus on developing relationships with corporate entities, investors and foundations that accelerate innovation related to digital health.

“We’ve set a road map for the next five to 10 years ahead,” said Entwistle. “It’s a dynamic process that will evolve as our ideas and thinking evolve, as the market changes, and as faculty and staff personalize it to their individual work areas.”

Meanwhile, the workgroup meetings have had a lasting impact. Since serving on the safety, quality and value workgroup, Christine Cunningham, administrative director of patient experience for Stanford Children’s Health, and her counterpart at the adult hospital, Alpa Vyas, vice president of patient experience, have drafted shared standards and goals for patient experience at both hospitals, and presented updates at the monthly committee meetings.

“Before this, Alpa and I would bump into each other at conferences and say, ‘We need to get together! We need to get together!’ and rarely found the time,” Cunningham said. “We are now forced — in a good way — to spend time together talking about how we’re different, how we’re the same and how can we look at the continuum of care together.”

Robert Harrington, MD, professor and chair of medicine, and co-lead on the workgroups for precision health and care delivery models, remarked, “Throughout the entire process of creating the integrated strategic plan, there was engagement of faculty and staff across all entities of Stanford Medicine. The discussions were data-driven and collegial, and all voices were heard. It was a great example of the collaborative working environment that is Stanford University.”

In 2017, the university began its own long-range planning process, which was an opportunity for the university

and Stanford Medicine to develop a shared future. The long-range plan builds on precision health and focuses on developing solutions with regional partners for preventive and population health. “The collaboration between Stanford Medicine and the rest of the university has really deepened in the past few years,” said Persis Drell, PhD, provost of Stanford University.

Together with the university, Singh embraces the idea of the three entities synchronizing their strokes. “When we’re all rowing in the same direction, can you imagine how much stronger we’ll be?” she said. “I think our impact and our ability to do more for human health, and for humans in general across the globe, will be even more powerful.”

STANFORD MEDICINE INTEGRATED STRATEGIC PLAN

HUMAN CENTERED AND DISCOVERY LED

OUR STRATEGIC PRIORITIES

Value Focused	Digitally Driven	Uniquely Stanford
<ul style="list-style-type: none"> Embrace a value-based culture. Provide a highly personalized patient experience. Ensure a seamless Stanford Medicine experience. 	<ul style="list-style-type: none"> Amplify the impact of Stanford innovation globally. Deliver human-centered, high-tech, high-touch care and revolutionize biomedical discovery. Lead in population health and data science. 	<ul style="list-style-type: none"> Accelerate discovery in and knowledge of human biology. Discovered here, used everywhere: advance fundamental human knowledge, translational medicine and global health. Ensure preeminence across all of our mission areas.

ENABLERS

<ul style="list-style-type: none"> Invest in our people and community. Embody value-driven operations. 	<ul style="list-style-type: none"> Build systems of intelligence. Optimize our collaborative environment. 	<ul style="list-style-type: none"> Strengthen organizational alignment. Seek innovative partnerships and philanthropic support.
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“We’re looking to change health care for the better, across the Bay Area, across the country, across the world,” Cunningham said. “The message I hope our patients, families and communities get is: We are one Stanford — even though we have different pockets and different tentacles — and these things are really important to us: to be uniquely Stanford, value-focused and digitally driven.”

For Minor, it’s a far step ahead from his first days at Stanford Medicine. “Several people who have been here for years have come up to me and said, ‘You know, the School of Medicine and the hospitals have never worked as well together as they are now,’” said Minor. “And that’s very meaningful to me. That holds promise not just for Stanford Medicine, but for all the lives we hope to improve.” **SM**

— Contact Julie Greicius at jgreicius@stanford.edu

THE FUTURE

human centered, discovery led

Can machine learning bring more humanity to health care?

COMPASSIONATE INTELLIGENCE

BY KRIS NEWBY

PHOTOGRAPH BY EDWARD CALDWELL

Stephanie Harman, MD, a palliative care physician at Stanford Hospital, has witnessed many people take their last breath, and she considers each passing a unique and sacred event.

She once saw a father look into the eyes of his adult daughter and say, “I love you so much,” then die seconds later. A hospitalized man with an aggressive cancer worked diligently to settle his affairs, then after he finished, paused for a few seconds and whispered in her ear, “Why am I still here?” Another daughter gently took her father’s hand and said, “Dad, I’ll be OK. It’s OK for you to go now.” The father obediently closed his eyes and passed away.

One morning Harman, petite with shoulder-length black hair and wearing a freshly pressed white coat, was called to the bedside of a 79-year-old man who had entered the hospital during the night with pneumonia. He had heart disease, diabetes and emphysema. He was on oxygen and an IV drip.

With a compassionate smile, she asked if he was up for a conversation. She knew an end-of life discussion needed to happen soon, but the family was too overwhelmed with emotions to broach the topic.

Harman began by asking, “What are your hopes if you can’t get better?”

The patient’s wife had recently had a stroke and he didn’t think she would be able to care for him

Palliative care physician Stephanie Harman, left, believes in helping people die on their own terms. A computer algorithm that informatics expert Nigam Shah designed to help predict hospital patient deaths enables palliative care teams to provide better end-of-life counseling.



at home. Yet he wanted to be with her during his last days, not in the hospital, even if that meant he might not live as long. He had no advance medical directive, a legal document that specifies who should make decisions for him if he became incapacitated. So, Harman, the primary care team and a palliative-care social worker spent hours helping him find a home hospice service that would support his medical needs and his own plan for the end of his life.

Harman's patient was fortunate; all too often patients die in an intensive care unit with unfinished business and missed goodbyes.

Harman is a co-leader of a Stanford pilot program that aims to change that. Each morning she receives a priority report from an intelligent computer program that, every 24 hours, analyzes which patients under the care of the general medicine physicians would benefit from palliative care. The tool helps her spend more time with patients and less on record reviews and, most importantly, it leads to better endings.

This is one of many Stanford Medicine projects that combine artificial intelligence technologies with medical expertise to help doctors make faster, more informed and humane decisions. They hope it will help them spend less time in front of computer screens and more time doing what they love: caring for patients.

THE DATA WRANGLER

HARMAN WAS FIRST INTRODUCED to the concept of AI in palliative care when Nigam Shah, MBBS, PhD, an associate professor of biomedical informatics, attended a hospital quality meeting in early 2017.

"I've developed a computer algorithm that predicts the likelihood of patients dying within 12 months," declared Shah, with a boyish face, a bulldog-like demeanor and onyx-black eyes that seemed to take in everything and everyone in the room. "Would you find that useful?"

Harman blinked, then said, "Yes. Yes. Physicians are terrible at predicting death."

Shah began developing a mortality prediction tool to help palliative care professionals identify patients who might benefit from having end-of-life conversations well before a medical crisis strikes.

Shah grew up in a small town in Gujarat, India's westernmost state, in an upper-middle-class family. His father was a surgeon who felt duty-bound to perform pro bono

procedures for the poor. His mother was a teacher and a school principal.

Shah planned to become an orthopedic surgeon and trained as a doctor, obtaining a bachelor of medicine and surgery degree from Baroda Medical College in Gujarat. But a family friend convinced him to pursue a PhD in the United States first. He landed at Penn State in 2000 and was so intrigued by the Human Genome Project, the mapping of the 3 billion nucleotide base pairs that make up human DNA, that he convinced his PhD committee to let him work on bioinformatics, the relatively new science of analyzing complex biologic data. For his thesis, he wrote a clever artificial

THIS IS ONE OF MANY STANFORD MEDICINE projects

intelligence program that predicted yeast behavior, and one of his PhD committee members suggested a way forward for him: "All the physicians who like artificial intelligence work at Stanford."

In 2005, Shah joined the biomedical informatics lab of professor Mark Musen, MD, PhD, at Stanford. The university had been applying artificial intelligence to health care problems since the 1980s, after setting up the legendary Stanford University Medical Experimental computer for Artificial Intelligence in Medicine, called the SUMEX-AIM. In the late 1990s, Musen and his colleague Mary Goldstein, MD, developed ATHENA, one of the first intelligent decision-support systems for managing patients with chronic diseases, such as hypertension. It's still in use at the Veterans Affairs Palo Alto Health Care System.

Stanford is also where three pioneers in statistics — Bradley Efron, PhD; Trevor Hastie, PhD; and Robert Tibshirani, PhD — developed algorithms to analyze complex data sets, laying the foundation for today's machine learning and data mining.

Stumbling into this AI hotbed just as electronic health records systems were taking off was the "aha moment" for Shah, who thought, "What if the evidence that physicians needed was buried deep within the vast, messy electronic health databases, and AI could help pull it out?"

"In hindsight this sounds like a brilliantly planned career trajectory, but it's nowhere close. It was a uniquely Stanford fluke," said Shah.

PREDICTING MORTALITY

SHAH BEGAN THINKING ABOUT mortality prediction while working with an advanced-illness management group at a nearby hospital. A cursory search of the medical literature confirmed his suspicion that physicians are woefully inaccurate at predicting how long terminally ill patients will live.

One of the best research studies on this topic asked 343 physicians to estimate the survival time frame of the patients they'd referred to hospice. Only 20 percent of the prognoses were accurate. What's more, the physicians overestimated survival times by a factor of five.

Deep learning is a technique that allows a software algorithm to automatically discover important factors from vast arrays of raw data. When it's "supervised," the algorithm is allowed to analyze variables associated with known outcomes so that it can learn from the past and apply its findings to future situations in a repeatable way.

In developing the tool, Shah first formulated a problem statement to guide his algorithm: "Given a patient and a date, predict the mortality of that patient within three to 12 months from that date, using electronic health record data of that patient from the prior year." Then he had it search and learn from the anonymized medical records of the millions

that combine artificial intelligence technologies with medical expertise to help doctors make faster, more informed and humane decisions.

The lead author of the study, Nicholas Christakis, MD, PhD, a professor of sociology and medicine at Yale University, went on to explore the reasons behind this over-optimism in the book, *Death Foretold: Prophecy and Prognosis in Medical Care*. He attributed this inaccuracy to "a complex set of professional, religious, moral and quasi-magical beliefs." Or, put more simply, the physician's innate desire to never give up fighting for their patients' lives.

To bring some objectivity to prediction, some doctors use palliative scorecards that assign weighted mortality scores to a patient's observable symptoms. One system rates walking ability, level of self-care, food and fluid intake, and state of consciousness. Another assesses weight loss, breathing problems and white blood cell counts. Yet another calculates a risk based on food intake, swelling of tissues, delirium and breathing at rest. And for use in intensive care units, the Acute Physiology and Chronic Health Evaluation 2, or APACHE-2, assesses acute physiology, age and chronic health conditions.

Shah had issues with all of the scorecards. Some used data sets that were too small. Some used oversimplified assumptions. Others narrowly focused on specific diseases or populations. He wanted a tool to predict the probability of death of *every patient* admitted to the hospital *every day*, by comparing their medical record to the millions of past patients of the hospital. So, he opened his artificial intelligence toolbox and settled on supervised deep-learning approaches to determine the most important predictors of mortality.

of patients who entered Stanford hospitals between 2010 and 2016, comparing past mortality factors with those of a newly admitted patient. For Shah's tool, the target outcome was a mortality prediction, and the variables included medical record entries such as an insurance code for a specific disease, a drug prescription or the pattern of visits. Here's how the system works:

Patient X is admitted at 9 p.m. At midnight, the algorithm looks at X's medical record for the past year and pulls out such features as age, gender, race, ethnicity, number of hospital admissions, disease classification codes, and billing and prescription codes. It aggregates those in groups over the past 30 days, 90 days, 180 days and beyond. The algorithm then compares Patient X's features with the combinations of features seen in millions of past patients and their subsequent outcomes. Finally, the software model calculates a probability of Patient X dying in the next three to 12 months.

The first set of results from Shah's algorithm were pretty good. Flags for high mortality risk included diagnosis codes of certain cancers and MRI and CAT scans, and multiple hospital admissions in a year. But there were obvious errors. A patient was put on the near-death list because an MRI scan was ordered under a brain tumor insurance code, even though the doctor later entered "No brain tumor" into the record.

But Shah didn't correct the inputs to the algorithm. "The algorithm needs to learn to handle such cases," he said, explaining that the algorithm would learn from its mistakes over time.

AI LOVE YOU

STANFORD ARTIFICIAL INTELLIGENCE PROJECTS DESIGNED TO IMPROVE YOUR HEALTH

ARTIFICIAL INTELLIGENCE WANTS TO MAKE YOU HAPPY. Streaming apps suggest music and songs based on your past choices.

Advertising apps note when icy white snow is piling up outside and tempt you with warm beach vacations.

Web mapping services suggest routes to avoid traffic jams.

Dating apps may even help you find true love.

Clinical researchers at Stanford Medicine are now using AI technologies to help you with another kind of relationship, the one with your doctor. These software algorithms are empowering your physician to deliver better, faster and more personalized medical advice to you. Here is a short list of these projects.

The Green Button project

PHYSICIANS CAN FILL OUT A SHORT ONLINE FORM and hit a green button to submit medical questions to specialists experienced in mining data within Stanford's 150 million-plus patient records for evidence-based advice. These experts use AI algorithms to answer a physician's question within seconds, followed by a live conversation to discuss the results. This saves time associated with manually searching medical literature for answers. Also, real-world evidence from the patient records answers clinical questions that aren't addressed in randomized clinical trials or medical guidelines. The service, which originated at Stanford, enables patients to receive personalized medical advice based on the experiences of people with similar health and demographic profiles.

Mining for hidden disease risk

RESEARCHERS HAVE DEVELOPED AN AI PROGRAM that can detect familial hypercholesterolemia, a rare genetic condition in which high levels of cholesterol in the blood result in a twentyfold increase in risk of coronary artery disease. By prescreening all patients at a clinic for this disease, high-risk individuals of this largely hidden disease can be treated early, avoiding serious complications such as heart attacks.

The researchers are exploring the feasibility of using this program for other diseases to provide cost-effective, population-level screening for conditions that might otherwise go undetected and untreated.

Updating heart attack, stroke risk data

A TEAM OF DISEASE PREVENTION RESEARCHERS RECENTLY USED AI TECHNOLOGY to update the data traditionally used to determine a person's risk of a heart attack or stroke. The old data included information about the health, treatments and outcomes of patients from more than 70 years ago. Researchers developed more accurate risk equations by extracting contemporary data from the records of more than 26,000 racially diverse patients, using sophisticated AI statistical methods.

"A lot has changed in terms of diets, environments and medical treatment since the 1940s," said Sanjay Basu, MD, PhD, assistant professor of primary care outcomes research. "So, relying on our grandparents' data to make our treatment choices is probably not the best idea."

The research suggests that 11 million Americans may need to talk to their doctors about taking different prescriptions of aspirin, statins and blood pressure medications.

THE VALUE OF PALLIATIVE CARE

AS SHAH WAITED for his deep-learning algorithm to hone its prediction skills, Harman continued to struggle with the day-to-day challenges of a palliative care physician.

She became interested in the specialty during her first year of medical school when her father-in-law was diagnosed with stage-4 lung cancer.

"The thing that stuck out in my mind was how he was able to die on his own terms," said Harman. Once it was clear that he wouldn't recover, he stopped treatment and

visited his family cabin in Ontario one last time, then died at home with hospice care.

"He was the first patient I ever pronounced dead," said Harman.

She thought that everyone died with such dignity, with their wishes honored, but after graduation, she realized it was the exception, not the rule. Studies show that 80 percent of Americans want to spend their final days at home, but only 20 percent do. She went into palliative care to help others experience death according to their wishes and to live well until that time.

“It’s terrible when you have to make decisions in crisis, because you may end up with medical care that doesn’t match up with what matters to you, and you won’t have time to think through the complex options.”

Palliative care physicians are able to discuss death with kindness and clarity in a way that can make some doctors feel uneasy. Doctors are often fighting for a patient’s life; a palliative care doctor is fighting for a patient’s quality of life.

But there’s a shortage of palliative care professionals in the United States. The National Palliative Care Registry estimates that less than half of the 7 percent to 8 percent of the admitted hospital patients who need palliative care actually receive it.

All of this factored into Harman’s desire to work with Shah on an AI model that predicts the need for palliative care.

“Ideally with this AI model, we’re identifying patients who are sicker than we realize,” she said. “And it gives us an excuse to say, ‘It’d be great if we could talk about advanced care planning.’ Or, ‘Have you had a discussion with your regular doctor about what matters most to you if and when you get sicker?’ I think the twist is that we’re using machine learning to add more to a patient’s care without taking anything away.”

THE NEED FOR TRANSPARENCY

THE TANTALIZING PROMISE OF being able to extract real-world clinical evidence faster and cheaper than the old ways motivates Shah to push his physician colleagues out of their comfort zone in embracing these new AI technologies.

“It bothers me that even in a well-studied field like cardiology, only about 19 percent of medical guidelines are based on good evidence,” said Shah. “Much of it comes from trials that have focused on 55-year-old white males. For the rest of humanity, physicians make a best-faith effort, enter it in the medical record, then never look back.”

Robert Harrington, MD, professor and chair of medicine and an interventional cardiologist, believes that AI can help fix this, saying, “Clinical trials tell you about populations, not about that patient sitting in front of you. This is where machine learning comes in. It allows you to look at large volumes of aggregated records from the recent past and create models that can assist with predictions about that one individual.”

The Achilles heel of today’s AI tools, however, is that they’re not that good at cause-and-effect reasoning. For example, an AI algorithm can’t tell if a rooster’s crowing makes the sun rise or the other way around. This is why having hu-

man experts involved in tool development is essential.

Case in point: When Stanford researchers first tested an AI tool for identifying cancerous moles, they were astounded at its accuracy. But when researchers analyzed the results, they identified a major flaw in the way they were training the algorithm: A large percentage of the cancerous mole photos had rulers in them. The algorithm drew the conclusion that rulers are a sign of cancer, not that physicians were more likely to use rulers to measure moles suspected of being cancerous. To correct this oversight, subsequent testing was done on photos without rulers in them.

The other risk with AI algorithms is that only clinicians with solid computer science know-how understand how they work, and this can lead to outcomes with unintentional biases or hidden agendas.

In the transportation industry, two news stories about algorithms with dark secrets buried in the code were described in a perspective piece that appeared March 15 in *The New England Journal of Medicine*: “A recent high-profile example is Uber’s software tool Greyball, which was designed to predict which ride hikers might be undercover law-enforcement officers, thereby allowing the company to identify and circumvent local regulations. More complex deception might involve algorithms designed to cheat, such as Volkswagen’s algorithm that allowed vehicles to pass emissions tests by reducing their nitrogen oxide emissions when they were being tested.”

In health care, the stakes are even higher. Non-transparent “black box” algorithms could be used to deny care to certain classes of people, overprescribe certain high-profit drugs or overcharge insurance companies for procedures. Patients could be harmed.

This editorial and another in *JAMA* on Jan. 2 are part of a larger effort by Stanford researchers to address ethical issues to reduce the risk of these negative consequences. The authors include Shah; Harrington; Danton Char, MD, assistant professor of anesthesiology, perioperative and pain medicine; Abraham Verghese, MD, professor of medicine; and David Magnus, PhD, director of the Stanford Center for Biomedical Ethics and professor of medicine and of biomedical ethics.

These experts warn that feeding biased data into an algorithm can lead to unintentional discrimination in the delivery of care. For example, the widely used Framingham Heart Study used data from predominately white populations to

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THE HIGH-TECH
AND HIGH-TOUCH GOAL
TO IMPACT
2 BILLION LIVES
BY 2025

BY JONATHAN RABINOVITZ

ILLUSTRATIONS BY JEFFREY DECOSTER

a global vision

An ambulance arrives to assist a woman in labor on the outskirts of Kathmandu and the emergency medical technician realizes there are complications he's not sure how to address. He quickly consults an application on his smartphone that offers guidelines on what to do.

Stanford emergency medical faculty anticipate that such a scene could be happening now, as the nonprofit Nepal Ambulance Service, or NAS, aims to support several dozen health workers who have completed the nation's first-ever EMT training program, developed by Stanford educators and their Nepali counterparts. Together, they developed the app and are now studying it to see whether it improves the EMTs' performance.

When NAS began operating in 2011, it was the first and only ambulance service available to the more than 1.3 million people in the Kathmandu area. Since then, it has carried more than 18,000 patients who have called its three-digit toll-free number — 102 — for help. It is modeled in part on a nonprofit in India, GVK Emergency Management and Research Institute, which has grown to be the world's largest ambulance system since its founding 13 years ago. In India, more than 750 million people can now access emergency services provided by some 47,000 EMTs, dispatchers, drivers and other workers who staff GVK EMRI's ambulance system.

Faculty in Stanford's Department of Emergency Medicine have been involved in both organizations from their beginnings, as well as with initiatives in Cambodia, Myanmar, Uganda and elsewhere. They have collaborated with Indian and Nepali researchers to assess patient needs, to set up referral networks and to improve quality of care. And they have not only authored the standard emergency medicine protocols for these countries, but also helped create a workforce to execute them.



These efforts to improve emergency care are part of an ambitious goal presented in Stanford Medicine's 2018 strategic plan: Dean Lloyd Minor, MD, and Stanford's Center for Innovation in Global Health aim to impact 2 billion lives by 2025 through its precision health approach. The challenge is how to make Stanford innovations in medical training and research accessible to the entire world. The answer is a combination of "high touch" and "high tech" to deliver new programs that draw on Stanford Medicine's acumen in providing patient-centered care and its expertise in collecting and analyzing data to devise better treatments.

The high-touch part of the equation involves making personal connections. "There is a need to have boots on the ground," said Michele Barry, MD, senior associate dean for global health and director of the center. "We want to help globalize the work of educators, researchers and practitioners at Stanford Medicine through strong partnerships with local stakeholders."

The global health center, which has a network of 170 faculty fellows, tracks more than 1,000 Stanford Medicine projects around the world. Every year it arranges for 50 Stanford physician-scientists to embed in programs overseas, and it provides seed grants to launch four to 10 pilot studies that often become major clinical, education and research endeavors.

The partnership between Stanford Medicine and GVK EMRI offers an example of how the high-tech part can work. In India, GVK EMRI receives an average of about 130,000 calls per day through its 27 call centers, providing demographic and clinical data that can be used for quality assessment of its operation. GVK EMRI and Stanford researchers have conducted more than a dozen relatively small studies — lasting four months at most and involving no more than 2,000 participants — about obstetric emergencies, chest pain, vehicular trauma, and other injuries and illnesses. They are also beginning to examine much larger data sets from hundreds of thousands of calls and to use new computational methods, such as machine and deep learning, to gain deeper insights.

A similar research infrastructure is beginning to emerge in Nepal, where the system also gathers information about its patients through initial intakes and follow-up calls with

EMTs. NAS is also using the new app to collect data about the types of situations where EMTs seek additional guidance. (A seed grant from Stanford's global health center funded the development of the app.) The app replaces hard-copy guidelines that were carried in ambulances but seldom used by EMTs. Now NAS can see if EMTs are looking to the guidelines for help and over time it may be able to pinpoint gaps in their training based on their use of the app.

"We're training the forefathers and foremothers of a new specialty that didn't even exist in most of the world just a few decades ago," said S.V. Mahadevan, MD, professor of emergency medicine, who brought Stanford Medicine into these partnerships and has led their training efforts. "The recent development of emergency medical services in low- and middle-income countries is arguably the greatest advance in medical care in the last 25 years because of the number of lives impacted."

Stanford Medicine's support in developing EMT capabilities is likely to expand into more countries, bringing it closer to reaching its goal of impacting 2 billion lives. While that number may initially seem impossible to achieve, when you consider other global projects combining touch and tech — particularly one underway in South Africa and another long-time initiative in China — you can see how the bar may not be as high as it first appeared.

making gains against hepatitis B in China

THE STANFORD MEDICINE EFFORT TO IMPACT 2 BILLION LIVES DID NOT EMERGE OVERNIGHT. Samuel So, MD, the Lui Hac Minh Professor of Medicine, for instance, has been pioneering partnerships with local health leaders around the world for decades in the fight against hepatitis B. He was one of only two foreign experts invited to speak in 2004 at China's National Viral Hepatitis Prevention and Control Conference, and he caused a stir when he submitted his talk's title: "Why eliminating hepatitis B and liver cancer should be a national priority in China."

"I was advocating for the government to treat this as the

'We want to help globalize the work of educators,



major health crisis it truly is,” said So, who founded the Asian Liver Center at Stanford in 1996 to address the high preponderance of hepatitis B among people of Asian descent.

It was one in a series of bold actions he has taken over the years to raise awareness of hepatitis B, a disease he says kills more people worldwide than either AIDS or malaria. He began combating the disease in the United States and has traveled throughout Asia to promote stronger prevention measures, but much of his effort has been devoted to China, which bears the world’s greatest hepatitis burden.

The hepatitis B virus, or HBV, can be transmitted sexu-

ally or through shared needles, though in China its spread is predominantly from an infected mother to her child during birth. The virus cannot be spread through casual contact, shared food or saliva.

People typically carry HBV for decades before it becomes active, causing liver cancer and liver disease. There is no cure, but vaccination can prevent HBV infection and early treatment can substantially reduce its deadly complications.

About 10 million people in China will die because of it by 2030 unless access to treatment is improved, according to a 2016 news release from the World Health Organization.

researchers and practitioners at Stanford Medicine through strong partnerships with local stakeholders.’

“If China develops a national program to

While the problem remains serious, China has made tremendous progress over the past three decades. So, who is a fellow at the global health center, and the Asian Liver Center have helped to turn the tide by demonstrating how to expand vaccination and treatment in a cost-effective manner.

China began pushing for all newborns to be vaccinated against HBV in 1992 and a decade later made the shots free for infants. Still, about 40 percent of youth ages 5 to 19 were not vaccinated. As a result, So’s Stanford team took part in an HBV vaccine pilot project intended to sway the Chinese government to administer catch-up vaccinations for unpro-

tected children. The pilot ran from 2006 to 2008 in Qinghai Province in the remote northwest of the country, vaccinating more than 500,000 children.

“We wanted to influence the government to do this for the whole country,” So explained. Stanford’s center provided education and outreach about the benefits of the vaccine, while the Qinghai government administered the shots.

So wanted to use the results from the pilot study to estimate the cost-effectiveness of a national catch-up program. He reached out to researchers in Stanford’s Department of Management Science and Engineering who determined that vaccinat-



eliminate hepatitis B as a public health problem, other countries will follow.'

ing the estimated 150 million unprotected children nationwide would prevent 8.2 million new infections and 65,000 deaths.

So showed Chinese health ministry officials that such a program would lead to a net cost savings of about \$900 million. Although it would cost more than \$500 million to launch, it would save \$1.4 billion through averting the expenses of treating HBV-related diseases. Shortly thereafter, China's government changed its policy to have free catch-up vaccinations for school-age children.

Over the past decade, So and colleagues have carried out studies showing that treating the estimated 90 million people living in China with chronic HBV infection would be cost-effective. They have also conducted media campaigns and worked with employers to end the pervasive discrimination in China against people infected with HBV. With support from a seed grant from Stanford's global health center, they have developed a tool for mobile phones to help physicians make treatment decisions.

And this summer they are conducting a pilot study of a strategy to eliminate transmission from mother to newborn. Some 50,000 newborns still become chronically infected annually from their HBV-positive mothers.

"If China develops a national program to eliminate hepatitis B as a public health problem, other countries will follow," said So.

encouraging breastfeeding to prevent infant mortality

ON A RECENT MORNING IN MARCH, MAYA ADAM, MD, A LECTURER AT THE MEDICAL SCHOOL, ran a focus group near Cape Town, South Africa, to evaluate the effectiveness of videos produced by Stanford's Digital Medical Education International Collaborative, or Digital MEdIC. Sixteen health promoters, who are called mentor mothers, discussed their experience using beta versions of the videos, which aim to promote breastfeeding. It is part of a campaign the South African government has been waging to encourage nursing to counter the nation's high rate of infant mortality.

One mentor mother told the group how she had been welcomed into a corrugated iron shack in her township where a baby had recently died. The baby's aunt, who lived there and was expecting a child, explained that her sister had feared that breast milk alone was insufficient; she had started to feed the baby solid food, along with nursing, when the baby was a few months old; the baby began to have diarrhea and gradually wasted away.

The mentor recounted that she took out her tablet computer, provided by the Stanford program, and showed the aunt a video about infant diarrhea: what causes it, how giving solids too soon can lead to problems and how exclusive breastfeeding for the child's first six months can prevent it. "This is exactly what happened to my nephew," the aunt said to her. "I am not going to let that happen to my baby."

The video, produced for South Africa's campaign, is a part of the larger Stanford program to globally scale up health education. According to the World Health Organization, there is a shortage of 7.2 million health workers. The need for new models to deliver health education is greatest in places that have limited access to physicians and other health professionals, said Charles Prober, MD, Stanford's senior associate vice provost for health education, who founded Stanford's Center for Health Education. "Sharing our expertise requires a new approach to how health care education is developed and delivered."

The center, which includes Digital MEdIC, offers 15 free courses through Stanford Online, the private online education company Coursera and other websites run by nonprofits and government agencies. Among the courses are classes for physicians and medical students on antimicrobial stewardship and placement of an arterial catheter, as well as lessons for the general public on maternal and child health and nutrition. More offerings are in the pipeline.

"We are looking to make Stanford's health care education content available to anyone, anywhere anytime," said Prober, who is also a fellow at the global health center.

Adam has spent the past year living in South Africa, working with nonprofits and government agencies to produce videos that support their work. "Our goal is to be something like a cross between the Khan Academy for health and Netflix,

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THE NEW PRECISION HEALTH AND
INTEGRATED DIAGNOSTICS CENTER SEARCHES
FOR WAYS TO PREVENT
DISEASE ENTIRELY

BY HANAE ARMITAGE

ILLUSTRATION BY MARK SMITH

stop it

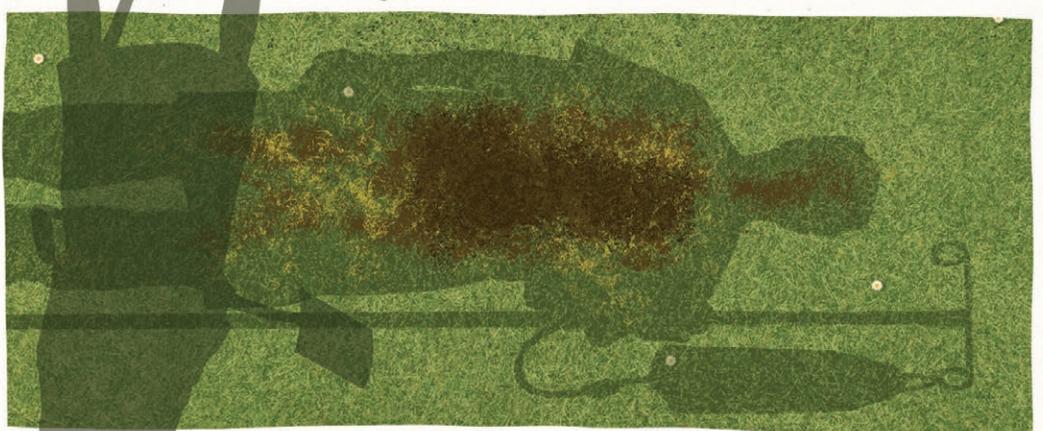
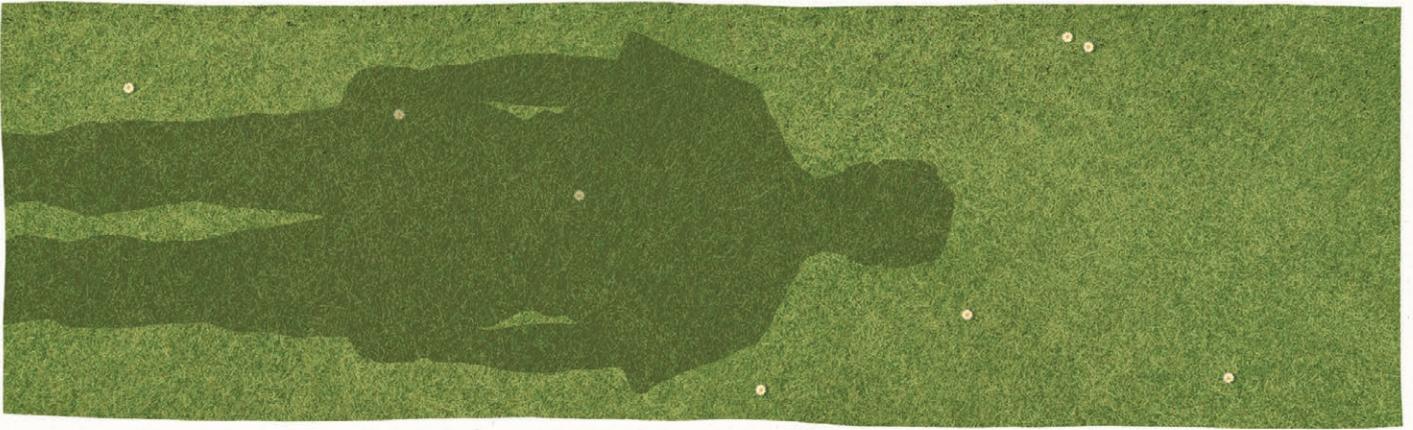
It's not often that world-class scientists band together to investigate disease with no intention of curing it. Yet upward of 55 scientists at Stanford's Precision Health and Integrated Diagnostics Center are doing just that in a push to get researchers and physicians off their heels and onto their toes in the battle against disease.

At the center, the goal is not to find a fix for the world's most pressing ailments; it's to detect them at their earliest stage, if not prevent them entirely.

"We want to be proactive, not reactive," said the center's director, Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology. "My thinking here was, 'What can we do so that the whole diagnostic field better aligns with precision health?' I think the way to get the biggest gain — although it will take several decades to play out — is to lead the charge on proactive research across multiple diseases in a broad-picture kind of way."

Established last year, the center, abbreviated PHIND and pronounced "find," backs dozens of scientists eager to test out some pretty nontraditional health-research ideas, such as nanosensor-equipped toilets that extract data from daily, um, deposits; bras that image breast tissue in search of abnormal changes; and a menstrual pad that can detect biomarkers of disease. But the central concept serves to ground the very philosophy of PHIND: using repetitive, precise measurements of individuals' health to make diagnoses earlier and ultimately stop disease before it causes real damage.

"PHIND is the only center to use precision health in such an enormous scope and scale," said Ryan Spitler, PhD, deputy director of the center. "We're looking at healthy and at-risk individuals to understand cardiovascular disease, cancer, neurological and mental health, and diabetes. In conjunction with those disease areas are the different ways in which you can



measure transitions from health to disease: wearables, implantables, data analytics and molecular mechanisms.”

The effort exemplifies Stanford Medicine’s focus on precision health under the leadership of Lloyd Minor, MD, dean of the School of Medicine.

The reality upon which all the PHIND projects hinge is often overlooked: Almost every person to ever fall ill was, at one point, healthy. So while other big research entities gun for the next breakthrough therapy, PHIND scientists put the transition to disease, rather than disease itself, under the microscope to prevent healthy people from becoming patients.

STOPPING THE ‘SPIKES’

One such scientist is Michael Snyder, PhD, professor and chair of genetics. More casually, he’s known as “the omics guy.”

Omics refers to the study of all the molecules in a particular biological sub-category in an organism — like all the genes, or all the proteins. Snyder and his collaborators are putting various omics profiles to work in a clinical trial that aims to prevent Type 2 diabetes.

They’re studying 100 people, all considered healthy but potentially prediabetic. Each participant receives a device to track and report glucose levels in their blood, around the clock. But the researchers also take samples of every participant’s microbiome (the mass of bacteria that mobs our gut) and metabolome (the collection of molecules produced during metabolism). They store these samples to examine later.

Snyder is looking for “spikers” — people whose glucose levels skyrocket after eating carbohydrates. A sharp uptick in glucose indicates that something is askew with either a person’s insulin — a hormone that helps the body turn carbohydrates into usable energy — or how that person’s body takes up glucose, and it’s a telltale sign of diabetes.

But insulin and carbohydrates are not the sole culprits of blood glucose booms. “The microbiome plays a big role in people’s glucose levels spiking,” said Snyder, the Stanford W. Ascherman, MD, FACS, Professor in Genetics.

“So what we plan to do with this trial is monitor each person’s glucose levels and the composition of their microbiome and their metabolome, then use this information to ideally piece together a diet plan that keeps their glucose levels under control.”

The key, Snyder said, is precision. “It’s not just ‘Don’t eat carbs.’ Different people spike to different things,” Snyder said. “I spike to bananas; you might be fine with bananas, but you might spike to rice. We need to pinpoint the dietary needs for each person.”

‘About 70 percent of prediabetic people become diabetic, and that’s why it’s so crucial to catch and manage these conditions before people even show symptoms.’

Snyder’s goal is to compile all of this information — glucose readings, microbiome and metabolome profiles — and use machine learning to prevent the onset of diabetes by not only predicting who’s at high risk for diabetes, but also by prescribing diets that harmonize with each participant’s metabolic tendencies.

“About 70 percent of prediabetic people become diabetic, and that’s why it’s so crucial to catch and manage these conditions before people even show symptoms,” Snyder said. “We think the PHIND center will be very powerful for understanding basic metabolic control. It’s one of the biggest problems out there, and we hope this project will help us better understand and control people’s metabolic function, especially in glucose control and diabetes.”

PREVENTING TEEN DEPRESSION AND SUICIDE

The beauty of precision health is that it can apply to nearly any field of biology, even the harder-to-pin-down ones, such as mental health.

In partnership with PHIND, Ian Gotlib, PhD, professor of psychology, is applying a rigorous approach to understand the many spokes that support psychological well-being, particularly as it relates to depression and suicidal behavior in teens. Gotlib’s goal is to compile neurobiological, molecular and experience-based information and use machine learning to predict which mixes of factors could predispose someone to dangerous, even life-threatening, behaviors.

“We know that adolescence is a peak period for the rise of depression, but we cannot predict these increases in depressive or suicidal behavior,” said Gotlib, who is the David Starr Jordan Professor. “We don’t yet have a sense of how to do that, which makes prevention difficult. So for the past five years my group has been conducting a comprehensive assessment of mental health in children and adolescents, and now with PHIND we’re empowered to go even deeper and consider new mental health factors for longer periods of time.”

Gotlib’s study follows 220 boys and girls from late childhood (ages 8 to 11) into their early teenage years (ages 13 to 16). In the first leg of the study, scientists interviewed children and their parents about the children’s stressful early life events — moving homes, parents’ divorces, witnessing violence, things of that nature. They also measured other aspects of stress, including cortisol levels, and assessed pubertal hormone levels and functional and structural brain connectivity.

Gotlib and his team are continuing to follow these adolescents into their teen years. With PHIND, they’re not only able to keep measuring parameters from the first part of the study, but also

able to buttress the data with new measures of inflammatory markers, high levels of which are often seen in people with depression.

They're even able to use data from watches that monitor activity and rest, and from the teens' cell-phones to tell if something is amiss. There's no spying going on here; they're not looking at the content of the phone, but rather the physical movements of the phone — how often it's used to send messages, how quickly the user responds to messages. (When things start to slow down, it can flag depression.) The teens' phones were also equipped with an app that prompts them to record information about their mood and activities in real time.

"We tend to neglect healthy people, but people aren't born with the disease state we're looking at," Gotlib said. "These things — depression, anxiety, suicidal behavior — develop through adolescence, and the only way to understand that development is to start with a sample of healthy people and study what the risk factors and biological signs are. This early detection and understanding the basics of the disease are central to PHIND's mission."

BLOOD-BASED CANCER CLUES

The need for quicker cancer diagnostics has researchers combing the genome for molecular hiccups indicative of the disease — whether it's how tumors start, spread or, ideally, how they can be stopped.

In a PHIND-funded project, Christina Curtis, PhD, assistant professor of medicine and of genetics, and Anshul Kundaje, PhD, assistant professor of computer science and of genetics, have turned to a simple blood draw, or liquid biopsy, to reveal cancer's most complex secrets. Curtis' goal: Use blood analysis as a tell-all source that not only flags the presence of cancer, but reveals where it came from in the body and if it's poised to infiltrate other organ systems. And she wants to do it all on an earlier timeline, with heightened precision.

It's a lot to ask of a run-of-the-mill blood draw, but Curtis and her group are devising a search tactic that goes beyond identifying rare mutations in DNA. She's looking at epigenomic footprints, types of markers typically embedded in DNA. While these markers are often found enclosed in the cell, Curtis takes advantage of cell-free DNA, which floats openly in the bloodstream after shedding from a tumor or from healthy tissues.

"We're taking a really different approach. We leverage epigenomic profiles, which contain information about which tissue the cell-free DNA is derived from and if it's cancerous," Curtis said. "And while certain mutations are important hallmarks of cancer, there's a unique profile that the epigenome provides,

'Science isn't often discovery out of nowhere. It comes out of fortuitous collisions in which different fields that don't typically communicate come together.'

including clues about the cell's activity or state."

Research from Curtis' lab shows that some cancers are born to be bad from day one; mutations and epigenomic factors render the cancerous cells aggressive, malignant and more lethal. Curtis hopes a blood-based analysis could detect that kind of cancer and its origination before the patient even shows symptoms. In that sense, it would work as a screen, she posits, that everyone could incorporate into their routine annual checkup.

That's still a long time away, Curtis said. But in her research, she's beginning to apply the blood-based technique to consenting cancer patients, working backward to test her technology's ability to pinpoint cancer types and aberrant signaling from cell-free DNA. So far, her preliminary research has yielded robust results.

"A big part of the challenge is that cell-free DNA in and of itself hasn't been deeply studied yet. What we're looking for here are really needles in haystacks — rare molecules that have been shed from somewhere in the body," Curtis said. "There's still a question surrounding what the makeup of a healthy individual looks like, so we're working on understanding that, too, because without that, we have no meaningful reference."

THE FUTURE OF PHIND

Technology, however, can advance only as far as researchers' understanding of biology enables it. "The smart toilet, which is being developed in my lab, can't work miracles if it doesn't know what to look for in the urine.

It's not a crystal ball; it has to know what biomarkers to detect," said Gambhir, the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research. "That's why we need more people on the basic biology side to understand the early changes as cells transition from normal to ill cells."

To this end, PHIND has doled out \$2.75 million to help catalyze basic, prevention-focused research at Stanford based on a competitive formal process. Some 20 projects were funded in the initial round. In May, the center announced the availability of an additional \$1.5 million in seed funding. The goal is to launch as many as 12 new research projects by the end of this year.

"Science isn't often discovery out of nowhere. It comes out of fortuitous collisions in which different fields that don't typically communicate come together," Gambhir said. "And that's what we want to facilitate with PHIND to empower the science behind precision health and earlier diagnostics of multiple types." **SM**

— Contact Hanae Armitage at harmitage@stanford.edu

RESEARCHERS AIM TO HARNESS MICROBES IN OUR
INTESTINES TO CURE WHAT AILS US

BY BRUCE GOLDMAN

ILLUSTRATION BY MIKE MCQUADE

the doctor is in... your gut

Think of the trillions of bacteria that live inside your gut as a medicine cabinet. The microbial ecosystem thriving in your intestine — what scientists call your gut microbiota — squirts druglike quantities of bioactive chemicals into your bloodstream every single day. Wouldn't it be nice if you could tailor their output to fit your prescription?

Each of us, when we're healthy, harbors perhaps 600 to 1,000 different strains of microbes (mostly bacteria) in our gut. Collectively, they can do all kinds of tricks. They not only help us digest our food, but also coach our immune system, provide energy, converse with cells in the intestinal lining and, by coating the mucous membrane on the inside of our gut, act as a protective lawn that provides a barrier to invading "weeds," aka pathogens.

They're also little drug factories. They excrete myriad metabolic byproducts, which become a cocktail of chemicals coursing through our blood. Many of these have bioactive properties, said Michael Fischbach, PhD, Stanford associate professor of bioengineering and institute scholar at Stanford ChEM-H, and some are produced in sufficient amounts to produce a druglike effect, for better or for worse.

"A single strain's chemical output can add up to as much as 200 milligrams a day," Fischbach said. "That's about the same as the amount of active ingredient in an Advil tablet."

There's growing evidence that the presence or absence of certain gut bacterial metabolites in a person's body can cause, contribute to or even prevent a range of health problems. Fischbach and other Stanford scientists from a variety of disciplines have shown that procedures as

simple as adding or subtracting a single substance produced by a single gut bacterial strain can have a substantial medical impact. They're developing tools to precisely define and manipulate our gut microbiota, or even individual genes within individual resident microbes. And they're working toward the creation of a defined "template" human gut microbiota that can serve as a scaffold for rebuilding our internal

complicate such simple designations.

But say we did know what's good for whom. The same microbial lawn that protects against pathogenic invasions makes it tough for even the most desirable of microbes to take root. It's never easy for a new kid moving into a new neighborhood already populated by battle-tested, streetwise residents who know their turf and know how to get exactly



microbial communities to cure or ameliorate disorders such as kidney disease, inflammatory bowel disease, obesity and heart disease.

A SINGLE SUBSTANCE CAN MAKE A BIG DIFFERENCE

MANIPULATING OUR GUT MICROBIOTA is hardly a new idea. People have been eating yogurt for millennia. The whole point of ingesting probiotics is, after all, to upgrade our collection of gut microbes.

But that's easier said than done. To begin with, we really don't know which microbes would be ideal candidates for gut-microbiota membership. The varying composition of people's gut microbiota, and the resulting difference in metabolic dynamics underway in different people's guts, could

what they need, when they need it and who to get it from.

So it's not surprising that probiotics are typically transient — within a day or two those freshly introduced bugs are already out of your system — or that their effect tends to be small and not highly predictable.

Fischbach and his colleagues have been taking steps toward what may prove in the long run to be a surer, more precise way to optimize a person's gut microbiota. He and colleagues are on what he describes as a "hunt for microbiota-derived molecules of interest."

This hunt can be exemplified by a study Fischbach conducted with Stanford colleagues Justin Sonnenburg, PhD, an associate professor of microbiology and immunology, Dodd Dylan, MD, PhD, an instructor in pathology, and several collaborators.

The scientists knew from previous studies that a gut-bacterial strain called *Clostridium sporogenes* is one of the few that can convert the chemical tryptophan, found in dietary protein, into a metabolite called indolepropionic acid, or IPA. Previous work had also suggested that IPA can strengthen the intestinal wall, preventing gut bacteria from getting into the bloodstream and possibly triggering a nasty inflammatory immune response — a characteristic feature of inflammatory bowel disease. IPA is also believed to be neuro-protective and has been considered a potential treatment for Alzheimer’s disease.

First, the investigators sought to determine the series of biochemical steps *C. sporogenes* takes to transform tryptophan into IPA, which was unknown. They used bioinformatics to nail down, for the first time, the genes coding for the enzymes involved in the tryptophan-to-IPA pathway. (Enzymes are protein machines that carry out virtually every biochemical transformation in a cell.)

“We’ve developed computational tools to sift through all the genes of the gut microbial community, and see just how a bug makes the molecules it’s making,” said Fischbach. A bioinformatics application called ClusterFinder that Fischbach developed, since merged into an application called antiSMASH, relies on the premise that all of the enzymes that can perform a specific type of biochemical conversion tend to feature similar to identical biochemical structural elements — and that therefore the genes that encode these similarly functioning enzymes will also have similarities. Another key tenet of this kind of bioinformatics search engine: Genes that work together in bacteria are physically clustered together on the bacterial chromosome.

Fischbach and his colleagues trained an algorithm — effectively a digital bloodhound — to find them.

Finding the relevant genes in the IPA-production assembly line made it possible to create a mutant *C. sporogenes* strain in which one of those genes was disabled so that this strain could no longer produce IPA but was otherwise virtually identical to the IPA-producing strain.

Now the team was able to install one or the other bacterial version in living laboratories known as gnotobiotic, or germ-free, mice. These mice are raised in a sterile environment and have never been introduced to any microbial species that could colonize their guts. Researchers can therefore colonize the mice’s intestines with one or a few microbial species of interest to see what they do individually or how they interact in pairs or small groups.

The researchers found that germ-free mice into whose guts the normal *C. sporogenes* strain had been introduced carried copious amounts of IPA in their blood, while those harboring the mutant non-producers had negligible amounts of circulating IPA.

“We were able to show that by colonizing a germ-free mouse with the mutant or wild type, you can effectively toggle on and off that important chemical,” said Dodd. In addition, the mice with IPA-rich blood had lower levels of inflammatory immune cells, as well as less-permeable intestinal walls — a good thing, because it decreases the likelihood of a gut bacterium going AWOL — than those whose bloodstreams were devoid of IPA.

Increased intestinal permeability contributes to the symptoms of inflammatory bowel disease, a debilitating condition that affects an estimated 1.3 million adults in the United States.

“If we could find ways of increasing IPA levels in these people’s bodies, via some combination of seeding patients’ guts with *C. sporogenes* and ensuring adequate tryptophan intake, maybe we could decrease the severity of their symptoms,” Dodd said.

This is a drop in the bucket, he added. “It’s one example among hundreds of bioactive microbial-produced molecules that are medically significant.” While most of those remain to be characterized, several others besides IPA have been fingered, variously, as healthful or harmful to humans.

ON THE MINUS SIDE, ON THE PLUS SIDE

IN A SERIES OF STUDIES over the past several years, Stanley Hazen, MD, PhD, chief of preventive cardiology at the Cleveland Clinic, and his colleagues have implicated gut bacteria in the production of a substance called trimethylamine N-oxide, or TMAO, which is detrimental to cardiovascular health.

Searching for circulating chemicals whose levels in the blood are better predictors of heart disease than those now in use, such as cholesterol or C reactive protein, Hazen came up with TMAO. High levels of circulating TMAO, Hazen’s group has shown, predispose people to atherosclerosis, kidney failure, heart attacks, strokes and death, via an assortment of biological mechanisms.

TMAO’s production is known to require specific strains of gut bacteria. Those mystery microbes metabolize dietary choline and carnitine found in meat, eggs and fish to an intermediate substance, which the liver converts to TMAO.

Might it be possible to bioengineer, say, a TMAO-producing bacterial strain so it no longer produces the stuff,

then introduce it to the gut in a way that allows it to outcompete the natural strain? That would allow us, as Russ Altman, MD, PhD, Stanford professor of bioengineering, of genetics, of medicine and of biomedical data science, has joked in reference to this goal, to “have our steak and eat it, too.”

Dodd said he, Fischbach and Sonnenburg are working on “figuring out what bugs make that troublesome intermediate and replacing them with doppelgangers that don’t make it.”

Generating the benign replacement strain or strains isn’t necessarily the entire solution, Fischbach added. There may also have to be some way of ensuring that whatever building blocks the “reformed” strain no longer metabolizes (and that could conceivably build up to toxic potencies themselves) get diverted to benign use instead. It may be necessary to introduce other bugs to slurp those up.

Back on the plus side, it’s known that various members of our gut microbiota can convert fiber — in essence, all the complex carbohydrates in our diet that we can’t digest, but that gut bacteria can — into substances called short-chain fatty acids that are a required energy source for cells lining our intestines and that, to boot, seem to exert a calming influence on our immune systems.

Stanford scientists led by Denise Monack, PhD, professor of microbiology and immunology, showed in a 2018 study in *Cell Host & Microbe* that propionate, a short-chain fatty acid produced as a metabolic byproduct by gut-resident members of the bacterial genus *Bacteroides*, protects lab mice against

peptic molecules” produced by our gut bacteria, “and who produces them.”

IN WITH THE NEW

THE INTESTINAL LUMEN OF A germ-free mouse is a great place to find out whether and how the manipulation of individual gut microbes, or specific genes in a microbe, can be tweaked to provide a medical benefit. But it raises a question: How does one stably introduce a single new species, however sculpted it may be to one’s nutritional or medical needs, into the immensely complex, fiercely competitive and — after millions of years of coevolution — incredibly clannish old-bug network holed up in the human lumen?

Paradoxically, it may turn out to be easier to just replace the whole gut ecosystem.

“We’ve learned some remarkable lessons from fecal transplants,” said Fischbach of the procedure in increasingly widespread medical use, in which the gut microbiota of a person with a health problem traceable to some fault in that ecosystem — say, infection by the deadly pathogen *Clostridium difficile* — is replaced by the microbiota of a healthy donor.

“The rate of adverse events is remarkably low,” Fischbach said. “I would have expected 1 in 100 or at least 1 in 1,000 recipients to have, for example, an immune reaction against the new bugs. But no! Not only that, the new microbiota often engrafts well. The recipient’s microbiota looks a lot like the donor’s did, even months after the transplant.”

‘We’ve developed computational tools to sift through all the genes of the gut microbial community, and see just how a bug makes the molecules it’s making.’

infection by *Salmonella* (whose people-infecting counterpart can cause typhoid fever or food poisoning) by diffusing into the pathogen’s cells and altering their acidity. The study authors suggest that boosting *Bacteroides* populations in the human gut may help control the spread of *Salmonella* and other pathogens.

“This is just the tip of the iceberg,” said KC Huang, PhD, associate professor of bioengineering and of microbiology and immunology, who was one of the study’s co-authors. “In the next few years, we may identify hundreds of such ‘thera-

This begets a counterintuitive, exciting conclusion, Fischbach said. “I would have thought it would have been easier to add or subtract one or two species to optimize a person’s gut ecosystem. But it might be simpler, from a stability standpoint, to replace the whole community.”

But fecal transplantation as currently practiced has its drawbacks. For starters, a potential donor’s gut ecosystem is an undefined combination of hundreds of microbial strains, some known and many of them unknown. So there’s no

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sparkling drug discoveries

ACADEMIC RESEARCH CATCHES FIRE

BY ROSANNE SPECTOR

ILLUSTRATION BY MARK SMITH

On a spring day last year, Jane Tseng, PhD, was visiting Stanford to make connections to aid her drug development quest. The drug would be based on discoveries made by Tseng and other researchers at National Taiwan University. The compound already looked promising for helping people with schizophrenia and two other neurological conditions, and she wondered if it could help others. But one condition the professor of computer science was definitely not interested in pitting the drug candidate against was autism.

“Because autism is a spectrum, it’s going to be hard to test a drug and show it helps. Very hard,” she said.

Still, when Kevin Grimes, MD, co-director of Stanford’s SPARK drug development program, asked her if she’d like to talk with a Stanford autism expert, she said yes.

“SPARK sparks things. I was at Stanford to get new ideas, so I talked with him,” Tseng said.

At home in Taiwan, Tseng is the director of the Drug Research Center of the College of Pharmacy at National Taiwan University. She’s known for figuring out how drugs interact with other molecules and how that can enable them to work as treatments. But in Taiwan, as in the United States, most academic researchers know very little about turning a discovery into a drug people can use.

That’s where SPARK comes in. The fast-growing program, founded in 2006 at Stanford, has given hundreds of academic researchers around the world training and connections to help get their ideas out of the academic realm and into doctors’ and patients’ hands. For most, it’s a rare chance to see their discoveries helping people in need, and sometimes even saving lives.



The program has also proved to be an engine of discovery, especially for innovative drugs that answer unmet needs. Most of the SPARK projects address child and maternal health, global health and orphan diseases, all sectors neglected by pharmaceutical development.

Of 89 projects Stanford's SPARK program has sponsored in its first decade, 42 have been taken up by companies for further development, with 22 of these making it into clinical trials. SPARK has started 11 other clinical studies, without company involvement, of previously approved drugs for new clinical indications. The result is 37 percent of SPARK projects advancing to clinical testing.

The effectiveness of the approach has been noticed around the globe, with 57 programs based on the SPARK model being launched by academic institutions and governments on every continent except Antarctica. And the program directors have created a network of like-minded scientists in academia ready to address global health challenges when they arise.

"SPARK exemplifies how those of us in academia can go beyond what is expected — which is to teach and write papers," said Daria Mochly-Rosen, PhD, the program's founder and co-director. "It's a very simple and effective way to make sure that the research we publish eventu-

ally impacts patients. For us not to harness this potential and not bring it back to society is just irresponsible. This speaks to many of us, who really want to help patients. I think that's why it caught fire."

ally impacts patients. For us not to harness this potential and not bring it back to society is just irresponsible. This speaks to many of us, who really want to help patients. I think that's why it caught fire."

The keys to SPARK's success, said Mochly-Rosen, are the outside-the-box ideas provided by university researchers and the mentorship provided by industry experts. She learned how important that mentorship is the hard way.

For her first two decades in academia, Mochly-Rosen was immersed in the lab, typical for a researcher exploring molecular interactions within and among cells. But when one of her discoveries seemed that it could be the basis of a drug to reduce harm from heart disease, she felt compelled

to see that drug become reality. And after the university's efforts to interest a company fell flat, she decided she'd form a company of her own. "How hard could it be?" she thought at the time.

Very, she discovered. She took a leave of absence for a year and ultimately succeeded, co-founding KAI Pharmaceuticals Inc. in 2002 (acquired by Amgen in 2011), but it was tough and go at times: "There was no transition in my life that was more dramatic, except maybe the birth of our first child. I knew nothing about drug development, about the rigor and intellectual challenge that drug development entails," she said.

A few years after returning full time to Stanford she started SPARK to help others make the transition — to conduct what's called in academia "translational research." Grimes, at the time KAI's senior director of clinical research, left the company to co-direct SPARK and teach a course about drug discovery with Mochly-Rosen, now the George D. Smith Professor in Translational Medicine.

Another reason for the popularity of SPARK is cost. It can be less expensive than the traditional way universities attempt to spur translational research, which makes the model feasible for institutions with fewer resources, such as the University of Zimbabwe, the site of one of the newest SPARK programs.

"The most common solution for an institution that recog-

'this speaks to many of us, who really want to help patients. I think that's why it caught fire.'

nizes the need to do translational research is to create an incubator," said Mochly-Rosen. An incubator is a facility with professional staff to advise the investigators on all aspects of taking an idea and maturing it. Some incubators also provide equipment and help with writing grants.

SPARK at Stanford has no special facility or equipment. What it has is a wealth of volunteer advisers from industry. The program supports about a dozen SPARK inventors, or SPARKees, with up to \$50,000 per year for two years to show "proof of concept" for each drug candidate. In other words, they start at the first step of drug development, clinical needs assessment, then move through stages, which include identifying the drug molecule and the molecules

it interacts with; optimizing the drug molecule; assessing toxicity, dosing, and the best way to deliver it, first in lab studies and sometimes even in human trials — all to make the case to industry investors that there's demand for the drug and that it will actually work.

"We de-risk the projects so industry doesn't have to," said Grimes.

At Stanford the mentoring happens every Wednesday evening, when several of the research teams give progress reports to the gathered advisers, Mochly-Rosen, Grimes and other SPARKees. Stanford's program has 200 advisers — pharma scientists and business leaders — and 30 to 40 of them show up on any given Wednesday. If a researcher needs to test an unwieldy molecule for toxicity, one of them has likely tried it before and can share the tricks and pitfalls. They also share little-known facts — for example, did you know that ferrets are useful models for studying how lungs respond to drug candidates?

"They give real-world experience. It's an opportunity to learn not only what succeeded in industry, but what failed — which is really unique," Mochly-Rosen said.

"In each meeting we also have multiple advisers on the same topic. You don't get just a single person's opinion." The industry advisers, who sign nondisclosure agreements, can also meet with the scholars one-on-one and help them connect with potential business partners once the project is ready to leave the academic nest.

Tseng's project, now in clinical trials, is a typical example of how the process works.

She learned about SPARK from the vice president of her university, who heard about her research project and told her she should join. The government of Taiwan supported the first SPARK program outside Stanford, basing programs at National Taiwan University and National Cheng-Kung University in 2013. Now, six universities in Taiwan serve as bases. Tseng liked the idea behind SPARK, applied for funding and was accepted as a SPARK Taiwan scholar. Like Stanford's SPARK, Taiwan's programs have weekly gatherings with advisers from industry and venture capital firms.

Tseng's research focus is molecular modeling. "Basically I design a molecule using algorithms," she said. "We can do fast and robust drug discovery on the computer nowadays. But I was pretty much clueless about commercialization, like most university basic science researchers."

She was leading a huge team — six principal investigators and their labs — working together to see whether a molecular interaction that seemed to control certain symptoms of schizophrenia could be the basis of the drug. The symptoms, known as the negative symptoms of schizophrenia, are decreases or losses of normal functions — for example cognitive abilities, speech production, emotional response and interest in social interaction.

"The people with negative syndrome with schizophrenia are like a stone, no interest in interacting with others. And there's no effective treatment," said Tseng, who is now director of Taiwan SPARK.

The project was spurred in part by findings by others that a common food preservative seemed to comfort patients and alleviate negative symptoms. Tseng considered the molecular structures and interactions while eating lunch, a soothing bowl of instant ramen soup. "I thought, wait a second, I'm pretty sure what I'm drinking right now is a soup containing that same preservative. So are you telling me that everyone who's homesick loves to eat instant noodle just for the preservative? It's a comfort food for nearly everyone. This gave me a clue," she said.

Eventually, she and her collaborators identified a molecule and the key molecular connection that modulates the neurological symptoms. Interestingly, the drug candidate acts on a complicated biological pathway involved in learning, memory and much else — a pathway that hasn't been explored much for antipsychotic drug targets.

The group tested the drug in a small clinical trial of seven patients and it seemed to be working well, but the team didn't know what to do next, Tseng said. Then the project was selected for the 2016 SPARK showcase, an annual event at the Bio Investor Forum, a major international biotech conference. At the showcase, SPARKees from around the world pitch their projects to potential industry partners or funders.

"I had to learn how to do pitching. To be honest, I wasn't even familiar with the term, so I Googled it," she said.

That was another learning experience. "I was very hesitant to say that, 'Guess what, we are starting the company.' I had the idea it was the right thing to do but it was very scary to think down that path.

"It's a different way of thinking," Tseng said. "I had to learn how to pitch my project to VCs and pharma, and at first it didn't really click. You have to get used to thinking from the very end to the very beginning. You have to learn how

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plus

EXPLORING THE REALMS OF MEDICINE AND HEALING

Never give up

SERENDIPITY AND PASSION PEG AN ELUSIVE ILLNESS

By Ruthann Richter

PHOTOGRAPHY BY EDWARD CALDWELL

AT THE PEAK OF HER ILLNESS, ARNA SHEFRIN SPENT 22 HOURS A DAY IN BED. THE NIGHTS WERE AGONIZING; she'd doze off around 11 p.m., waking up a few hours later, crying out in pain. She tried to distract herself by listening to podcasts and watching videos on her iPad, while her husband shuttled to and from the kitchen for ice packs to help soothe her inflamed joints.

Severe anemia sometimes left her too weak to speak. A rash covered much of her body. She rarely ventured out of her home in Menlo Park, California, except for doctors' visits and a weekly bridge lesson. Though her thinking was foggy, she resolved to find answers to her mysterious condition, and she spent rare, lucid moments scouring the medical literature and preparing questions for a succession of specialists who were unable to offer answers or relief.

"Anger is a powerful motivator," she said. "I became irritated with my clinicians whom I felt were unable to help me but were letting me wither. If they were not going to help me, I would have to help myself. My focus became trying to get answers for what was wrong with me."

Shefrin's illness would take her on a yearlong odyssey seeking an explanation for her bizarre set of symptoms. Her persistence, as well as a stroke of serendipity, eventually led her to a pair of experts at Stanford.

It began in the fall of 2016 as Shefrin celebrated a highlight of her career, when she was named a distinguished alumna of the School of Dental Hygiene at the University of Manitoba in Winnipeg, Canada. At a gala dinner in her honor, a sea of health care practitioners gathered to acknowledge her contributions to the



ARNA SHEFRIN, PICTURED WITH HER HUSBAND, HERSH, WAS NEARLY INCAPACITATED FOR ALMOST A YEAR BEFORE HER MYSTERIOUS ILLNESS WAS DIAGNOSED.

profession as clinician, educator and clinical researcher.

It had been a stressful visit, but on the flight home, Shefrin began to relax and took a brief nap, only to be awakened by a sudden pain in her left hip, which felt like it was on fire.

"I had never experienced such intense bone pain in my life. I was in agony," she recalled. "Almost instantly, I went from healthy, though under a lot of stress, to being incapacitated."

The pain persisted, and a week later she broke out in a rash of splotchy, red welts that covered her from neck to toe and became a persistent irritant.

In a matter of months, Shefrin, a once-vibrant and creative woman, became bed-bound, mentally confused and tortured by pain, amid dramatic changes in her immune system. She refused to see friends — she didn't have the energy — and became increasingly dependent on her husband.

"I was always in bed. I had accomplished so much in my life. Yet here I was, trapped in bed. I couldn't think. I could barely talk," she said.

Shefrin, 68, is soft-spoken and slender, with silvery gray curls and an artistic flair: She designs and makes most of her distinctive clothes, some of which are sold in local boutiques. After her years in dental hygiene, she managed clinical trials at Syntex Corp., contributing to FDA approval of two major painkillers — Aleve and Toradol — and wrote extensively on the ethical and regulatory aspects of clinical investigations.

After her return from Canada, she contacted her primary care doctor at a community clinic, who ordered a series of blood tests. These indicated several abnormalities, including a very high platelet count — cells that help form clots and minimize or prevent bleeding. A normal platelet count can range from 150,000 to 400,000 cells per microliter of blood. She had at least twice that number.

"I was really scared," she said.

She was referred to a hematologist, who found that she also carried a mutation in a gene known as JAK2, or Janus kinase 2. Together with the high platelet

count, the finding persuaded the hematologist that Shefrin had a form of blood cancer known as essential thrombocythemia, which can cause clotting and bleeding problems. It seemed logical, given that about half of ET patients exhibit the JAK2 mutation.

But the diagnosis did not explain her rash, bone pain or low hemoglobin, a component of red blood cells, which eventually turned into severe, chronic anemia. It also didn't account for some other abnormal blood results, including an unexplained finding of monoclonal gammopathy, a condition in which white blood cells run amok, producing a single antibody over and over again, sometimes as a prelude to cancer.

Nonetheless, the ET diagnosis prevailed during most of her illness, though Shefrin was never convinced it was accurate.

A CONSTANT SUPPORT

ADDING TO her health concerns, on the same day in January 2017 — a Friday the 13th — that she was diagnosed with the blood disease, her gynecologist delivered another blow: She had a malignant tumor in one of her breasts.

"It was awful, one of the worst days of my life," Shefrin said.

Her husband of 48 years, Hersh Shefrin, took time from his job as a finance professor at Santa Clara University to care for her. He ran the house, shopped for groceries, and cooked for his wife (who had studied at the famed Cordon Bleu culinary school in London), trying to prepare meals that would appeal to her meager appetite. A "born nurturer," he was her constant support, attending all medical appointments and taking copious notes while trying to main-

tain an upbeat outlook in the face of tremendous challenges, she said.

"My job was to make sure she knew there was light at the end of the tunnel and to relieve as much stress as possible so she could focus on healing," said her husband, who is a pioneer in behavioral economics. "I am a decision theorist and economist. I know from my research that if you are optimistic, you cope better. My being up could help her be up."

He was on call 24/7 and rarely slept through the night, as Shefrin's symptoms were most intense at that time. He called them "nights of pain, interrupted by sleep." She took Tylenol and sometimes low doses of oxycodone, but knew from her research to be wary of the opioid's addictive potential. Her husband prepared middle-of-the-night snacks — pasta, cabbage salad or fruit — to keep up her energy. And he seized on the positive: "It will get better," he told her. "You may not see the light yet, but it's there."

During the day, she often fell into an exhausted sleep, while her husband retreated to his home office to work, priming himself with coffee to stay awake and keeping one ear open for a cry for help.

"If I didn't have a husband who cared, as he did, I would have said, 'What is the point?' I was in so much pain. ... He was counting on me to get better," she said.

He proposed little diversions to counter her misery. "I dreaded the weekly blood draws," she recalled. "He'd say, 'Let's go and get it out of the way, and then we'll go for a short walk afterwards.'"

After Shefrin's breast cancer diagnosis, she needed surgery to remove the tumor. That had to be delayed a couple

If I didn't have a husband who cared, as he did, I would have said, "What is the point?" I was in so much pain. ... He was counting on me to get better.

of times because she didn't respond well to chemotherapy to bring down her platelet count, a measure taken to avoid the serious risk of a blood vessel blockage or a bleeding problem during the operation.

The surgery finally happened in April 2017 and was followed by six weeks of radiation therapy. But she hit a new low just after her final treatment, when symptoms of what she thought was a urinary tract infection worsened. "I lay down on the bed, and I said, 'Hersh, call the doctor. I think I'm dying.' ... I can't remember ever being so sick. I was confused, I had severe vertigo, and I couldn't sit up."

That's when she first went to Stanford Hospital, where she was treated for dangerously low sodium levels, thought to be associated with treatment for the urinary tract infection. Clinicians there investigated many possible reasons for her condition, including metastatic bone cancer. The weeklong stay proved to be a turning point when she met Bernice Kwong, MD, a clinical associate professor of dermatology. Kwong was called in to help treat Shefrin's rash and ultimately became instrumental in piecing together the puzzle of Shefrin's disease.

While in the hospital, Shefrin was encouraged to follow up with a Stanford hematologist. But she hesitated, having already seen four hematologists elsewhere, none of whom could explain or effectively treat her condition.

"The clinicians would say, 'Our time for today is over. We'll see you in six weeks.' Then I would ask, 'What's the treatment plan?'" she said, her quiet voice rising in frustration. "Despite my polite and respectful questioning of my

doctors, I never had a treatment plan that addressed all my symptoms."

TRYING TO EXPLAIN SYMPTOMS

DESPERATE FOR ANSWERS, SHE finally worked up the energy to make an appointment with Jason Gotlib, MD, a professor of medicine who specializes in bone marrow diseases in which patients overproduce certain kinds of blood cells. By then, it was late August and Shefrin was 11 months into her illness. Gotlib, a genial clinician with an easy manner, recalled Shefrin's frustration when they first met.

"She was just completely handicapped" by her symptoms, he said, also recalling having doubts about her diagnosis. "My first impression was that her clinical presentation didn't fit with ET."

His skepticism rose when he saw that her lab findings showed extremely low hemoglobin, elevated white blood cells and 10 times the normal amount of C-reactive protein, a blood marker for increased inflammation and infection. Her erythrocyte sedimentation rate, a red blood cell test that also shows levels of inflammation, was off the charts, he said.

Gotlib said some of Shefrin's symptoms, including the anemia, the inflammation and the higher-than-normal white count, could not be solely explained by ET. "I said to her, 'You have the JAK2 mutation, which suggests ET, but something else is going on. And, by the way, what is this unusual rash?'"

That rash prompted Gotlib to refer Shefrin back to Kwong, who directs the Supportive Dermato-Oncology Program at the Stanford Cancer Center and with whom he often works on cases involving cancer patients with skin problems.

It was then that Shefrin sensed a positive shift. "Hersh and I left with so much hope because Dr. Gotlib said, 'We're going to get to the bottom of your illness. What you have is a puzzle, and I like to solve puzzles.'"

When Shefrin visited Kwong a few weeks later, the dermatologist immediately recognized her from her earlier hospital stay.

"She had the same rash, but this time, in addition to trying to treat the symptoms of the rash with medications, our interest shifted to trying to think about how this rash might help shed light on everything else that was going on with her health," Kwong recalled. So late that evening, after she put her three children to bed and made their lunches for the next day, Kwong sat down at her computer in her Palo Alto home and reviewed everything in Shefrin's lengthy medical record.

"Deep in her chart I noticed she had this monoclonal gammopathy that had been detected a year before and was thought to be of undetermined clinical significance. And I knew from our examination she had urticaria [rash]. At that moment, I knew I had to find out if she had arthritis or bone pain," she recalled.

That connection harked back to a single moment in Kwong's residency training at Stanford in 2009, when she was cramming for her dermatology boards. After clinic hours and between patients, her senior resident, Kerri Rieger, MD, PhD, now a clinical associate professor of pathology and of dermatology, would frequently give her pointers for memorizing thousands of facts, many of them very unusual, that might be relevant in her practice years later.

When they came to a rare disease known as Schnitzler syndrome, characterized by bone pain, a rash and monoclonal gammopathy, Kwong struggled to ingrain this trio of symptoms into

'Hersh and I left with so much hope because Dr. Gotlib said, "We're going to get to the bottom of your illness. What you have is a puzzle and I like to solve puzzles."'



PHYSICIAN JASON GOTLIB SAID HE DOUBTED HIS PATIENT'S FIRST DIAGNOSIS, BUT HE CREDITED DERMATOLOGIST BERNICE KWONG, LEFT, WITH UNRAVELING THE MYSTERY.

her brain. “Kerri told me she struggled too, but I am so grateful that she shared with me how she remembered the three symptoms. She taught me to picture a man by the name of Schnitzler, who had bone pain, urticaria and a monoclonal gammopathy. She drew me a picture of this man and gave me the mnemonic which allowed me to successfully memorize the associated findings,” Kwong said. “I remember thinking at the time, ‘Is this disease real? Is it ever going to matter that I remember these little details? Will I ever see this in my life?’”

Now it was real, and the details mattered intensely. She asked Shefrin to return the next day for a small piece of skin to be removed from her arm for evaluation. The results showed that her skin was loaded with neutrophils, specialized white blood cells that are among the first responders to inflammation. Neutrophils frequently accompany a rash, Kwong said, but when combined with bone pain and monoclonal gammopathy, the cause can be Schnitzler syndrome, a very rare auto-

inflammatory disease afflicting only about 300 people in the world. Kwong, exuberant, phoned Shefrin at home.

“She said, ‘I think I know what you have! And there is a treatment for it.’ I was overcome with emotion,” Shefrin recalled.

TESTING THE DIAGNOSIS

THE SYNDROME was first described in 1972 by French dermatologist Liliane Schnitzler, MD. There is no known marker for the disease, which is diagnosed on the basis of a set of symptoms that include those Shefrin had. In fact, hers is a textbook case. The ultimate diagnostic test, however, is whether patients respond to treatment. Standard therapy involves using the rheumatoid arthritis medication, anakinra, which counters the effects of the inflammatory molecule, interleukin-1, thus suppressing the inflammation, which is at the core of the disease. It’s expensive, with an average wholesale price of \$167 for a daily dose.

On Nov. 7, 2017, 14 long months

after her symptoms first appeared, Shefrin began using the medication, injecting a single dose into the skin of her abdomen around 3:30 that afternoon.

“By 4 p.m., the rash was disappearing. The pain, which always appeared around 4 or 5 p.m., was on its way, when suddenly, it stopped,” she said. “When I woke up the next morning, the rash was completely gone. It was truly a miracle. I’ve had no pain since.” As Shefrin continued to inject herself daily with the medication, she slowly began to regain her energy, and her blood tests gradually approached normal.

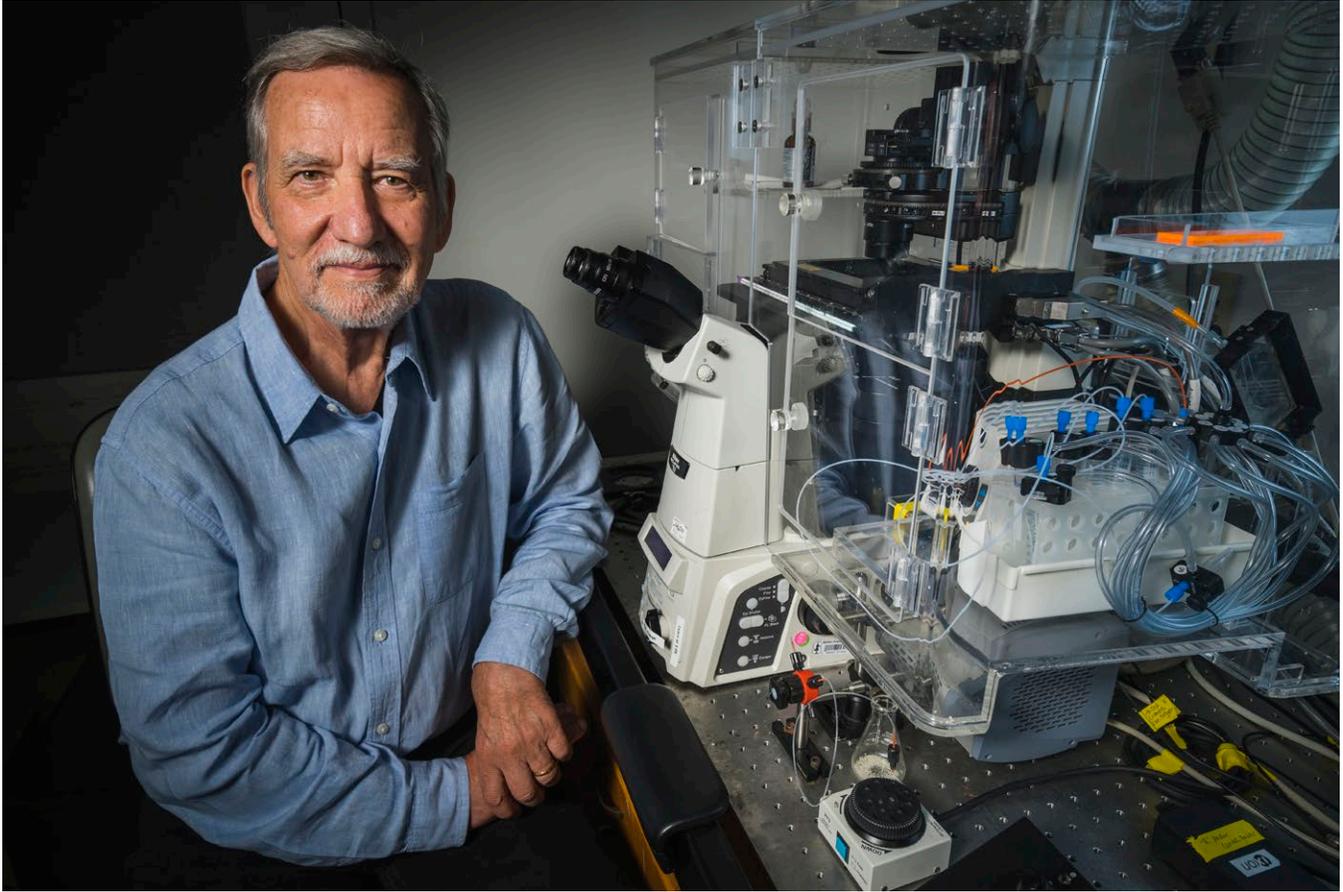
“Her life is back. It’s unbelievable,” Gotlib said. “If I look over the last few years, I think this is one of the cases I’m most proud of. Right from the start, I had a degree of skepticism about what was going on. However, Bernice is the one who put it all together.”

Shefrin was Gotlib’s first Schnitzler patient but Kwong had a patient a few years ago who, in retrospect, she believes also had the disease. That woman suffered for 25 years with intense pain no rheumatologist could remedy, Kwong said. However, after starting anakinra treatment, the woman was able to return to gardening, her passion. Kwong and Gotlib both now agree that the disease is vastly under-recognized by physicians. They remain on alert for detecting other patients.

Kwong said she will never forget Shefrin and her case.

“Those moments make you step back and think, this is why I’m here — to help people in the darkest moments of their lives and to try to find some light and some answers,” Kwong said. “I’m so grateful to be in an academic center, where I have colleagues like Jason who can say, ‘Can you see this patient one more time and look at her symptoms from a different angle?’”

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Inside help

STANFORD RESEARCHERS LAUNCH A MASSIVE STUDY OF LUNG TISSUE — HEALTHY AND DISEASED — FROM ONE OF THEIR OWN

By Krista Conger

PHOTOGRAPHY
BY EDWARD CALDWELL

WHEN RESEARCHER JAMES SPUDICH FOUND OUT HE HAD LUNG CANCER, HE OFFERED HIS COLLEAGUES A CHANCE TO EXPAND THEIR KNOWLEDGE BY STUDYING HIS TISSUES.

IT WAS AROUND 3 P.M. ON A THURSDAY last October when James Spudich and Suzanne Pfeffer poked their heads into the office of Mark Krasnow, on the fourth floor of the Beckman Center for Molecular and Genetic Medicine, interrupting a meeting he was having with a colleague.

“Can we talk to you for a minute?” Pfeffer asked.

Impromptu conversations were nothing new for the three. The longtime colleagues and friends have a lot to talk about. They’re all professors in Stanford’s Biochemistry Department and have worked together for decades. All three have chaired the department, with Pfeffer, PhD, in her second stint in that role.

But this time, the topic was more personal. Spudich, 76, had come to share some unexpected news: He had lung cancer. “I was wondering if you were looking for any human tissue samples for your research,” he said.

Shocked and saddened, Krasnow asked when Spudich would undergo surgery to have the tumor removed.

“I told him it was scheduled for 8 a.m. the next morning,” Spudich, PhD, recalled. “I remember Mark went kind of pale.”

Spudich had no way of knowing it, but the meeting he'd interrupted between Krasnow, MD, PhD, and assistant professor of pediatrics Christin Kuo, MD, had been called to discuss how Krasnow could broaden his research, which he had been conducting mainly in mice and small primates called mouse lemurs, to include human cancers. But the logistical and legal hoops that would need to be cleared prior to any kind of human-based research were daunting, and Krasnow knew it would likely take months to obtain the necessary approvals.

Kuo, a specialist in pulmonary medicine, had been working with Stephen Quake, PhD, co-president of the Chan Zuckerberg Biohub, and Spyros Darmanis, PhD, at the time a postdoctoral scholar and now a group leader at the Biohub, to study the development and function of neuroendocrine cells in the lung using single-cell RNA sequencing. These cells release hormones into the blood in response to signals from nerve cells. As a pulmonary fellow, Kuo had worked with Krasnow to conduct her initial studies in mice. But in 2016 she'd established her own laboratory in the Department of Pediatrics and had begun to develop the methods and key chemical components necessary to efficiently isolate human lung cells. Not only did she have all the necessary protocols and approvals in place to begin her study, she had also already established a collaboration with Joseph Shrager, MD, professor and chief of thoracic surgery, who was slated to perform Spudich's procedure the next morning.

Within moments, the researchers had initiated a remarkable series of events that would, over the next 16 hours, lead to the beginning of what will likely be the world's largest study of healthy and diseased human lung tissue. Dubbed the "lungome," the effort

has brought together researchers and clinicians from throughout the Beckman Center, Stanford Bio-X and the Biohub to perform a kind of unprecedented molecular poking and prodding of Spudich's lung tissue — analyzing gene expression profiles, signaling pathways, cellular architecture and immune responses — to identify for the first time exactly what goes wrong when lung cells become cancerous.

'A REMARKABLE STORY'

DESCRIBING THE significance of the research, Krasnow said, "This is a massive attack on a human disease with the most modern of research tools on one tumor from one patient. In five or 10 years, I believe that the knowledge from this study will guide the standard of care for all lung adenocarcinoma patients. It's a remarkable story."

The effort isn't intended specifically to help Spudich, whose prognosis is good because his cancer was caught early and removed quickly. Rather, it promises to offer an intimate glimpse into the earliest steps of cancer development in human lung tissue and will likely lead to better diagnosis and treatment of lung adenocarcinomas — a subtype of lung cancer that accounts for nearly half of all new diagnoses.

In the hours leading up to the surgery, the researchers struggled to balance their excitement about the scientific opportunity with their concern for a colleague. To say James Spudich is well-known in the Stanford Medicine community would be an understatement.

Many of the more than 20 people involved in this last-minute research effort have known Spudich for years. Quake, professor of bioengineering and of applied physics, received a bachelor's degree

in physics at Stanford in 1991 and had done postdoctoral work under professor of physics Steven Chu, PhD. At the time, researchers in the Chu and Spudich labs were collaborating to build a single-molecule laser trap that Spudich would use to study the molecular motors necessary for muscle contraction. (Chu was awarded the Nobel Prize in physics in 1997 for related work.) Together, Chu and Spudich launched Stanford Bio-X in 1997 to promote interdisciplinary collaborations between researchers in Stanford's schools of Medicine, of Engineering and of Humanities and Sciences.

Nearly everyone speaks of Spudich with admiration, not just for his prodigious scientific accomplishments — he received the 2012 Albert Lasker Basic Medical Research Award for his research into the molecular motors that drive muscle contraction — but also for his warmth and kindness.

"Everyone knows and loves Jim," Quake said. "So it wasn't surprising that our whole community mobilized immediately to make this happen."

"This was an amazing scientific opportunity that came much earlier than expected," said Krasnow, who is also a Howard Hughes Medical Institute investigator and the Paul and Mildred Berg Professor. "But, of course, there was also the realization that

we were talking about our beloved colleague, mentor and friend. When that person is right in front of you, and with you, it gives this effort an urgency and a poignancy that brings science and medicine together in such a beautiful and powerful way."

Spudich, who refers to the effort as Project Lung, is far less sentimental. In fact, some might say he's unabashedly enthusiastic. "There's no place else in the universe where the biology, the biophys-

Everyone knows and loves Jim. So it wasn't surprising that our whole community mobilized immediately to make this happen.

ics and the technology — everything that we can muster to throw at these tissues — exists that will allow us to really understand the lung in unprecedented molecular detail,” Spudich said. “What is going to emerge is an understanding about lung biology at a level of depth no one has previously imagined. And it’s kind of special that this is my lung.”

COMMON FORM OF LUNG CANCER

LUNG ADENOCARCINOMA IS THE most common type of lung cancer. It usually occurs in current or former smokers, but it is also the main type of lung cancer in nonsmokers. It’s frequently diagnosed at a late stage, after patients report symptoms of coughing or other vague symptoms like weight loss or unexplained pain.

Spudich was lucky that his cancer was discovered early. “I was at my annual physical on Sept. 20, 2017, when my doctor asked how I was. I said I felt great, but my wife, Anna, said, ‘No, he’s not alright,’” Spudich recalled. “We looked at her, and she continued, ‘Jim’s more tired than he usually is, and he has a slight cough, and we just came back

from India.’ I felt both of these symptoms were unremarkable, as I’m getting older, but heeding her concern, my doctor ordered a chest X-ray.”

The X-ray, taken nine days later, showed a slight cloudiness in the upper lobe of Spudich’s left lung. Subsequent CT and PET scans suggested the presence of a possible adenocarcinoma, about 2 centimeters long, which was confirmed by a biopsy. Surgery to remove the lobe, containing both normal and cancerous tissue, was scheduled for the morning of Oct. 27.

“So, totally unexpectedly, I went in one month from feeling normal and fit to having to deal with lung cancer,” Spudich said. “I knew it was time to talk to Mark, who is the world’s expert on lung development and who was carrying out some of the most cutting-edge research on the origins of lung adenocarcinomas in laboratory mice.”

At the time, Krasnow was part of a large collaboration organized by Quake and Tony Wyss-Coray, PhD, professor of neurology, to understand the diversity of cell types in many tissues as part of the Chan Zuckerberg Biohub’s

Cell Atlas project. Using technologies developed by Quake and others, researchers are performing comprehensive profiling of the total set of RNA molecules in individual cells, enabling them to analyze cell type and state with unprecedented sensitivity and precision in both health and disease.

“Steve [Quake], Tony and their teams were working on a mouse cell atlas,” Krasnow said. “We were in charge of the lung aspect. We had been assembling what we termed ‘rapid response teams’ to quickly collect and analyze the mouse tissue. So we knew how to do something like this, and how to do it well. But we hadn’t done it before in humans, and nowhere nearly as quickly as we had to act with Jim’s tumor. Normally we had a lead time of days or weeks; now we had hours.”

‘A UNIQUE OPPORTUNITY’

IN ADDITION TO ensuring all aspects of the protocol were followed, including explaining to the patient, Spudich, exactly what would happen, Krasnow faced another hurdle: how to get funding for the surprise project.

“I immediately contacted Steve and described how this was an amazing opportunity to extend the CZ Biohub studies in mice into human lungs and lung cancer,” Krasnow said. “We could analyze normal and diseased human tissue, and compare it to what we had learned in mice and mouse lemurs. And then I told him who the patient was. I don’t think it took Steve even a second to say, ‘Go for it.’”

CZ Biohub collaborators, including director of genomics Norma Neff, PhD, and scientist Lolita Penland, PhD, quickly pitched in, dedicating time and resources. “Collaborating with CZ Biohub provided the genomic expertise and sequencing platforms necessary to analyze tens of thousands



ANALYZING TISSUE FROM A COLLEAGUE ALLOWED BIOCHEMISTRY PROFESSOR MARK KRASNOW AND HIS TEAM TO, FOR THE FIRST TIME, FIND OUT EXACTLY WHAT GOES WRONG WHEN LUNG CELLS BECOME CANCEROUS.

of cells from the tumor, an unprecedented feat in terms of scale and resolution,” said graduate student Ahmad Nabhan, who coordinated the effort with graduate student Kyle Travaglini.

That afternoon, members of the rapid response team, including Kuo, Nabhan, Travaglini and postdoctoral scholar Astrid Gillich, PhD, went to work to “humanize” their mouse studies. “Christin worked on the clinical side,” Krasnow said, “getting forms and making connections with surgeons, clinicians and pathologists. Meanwhile, the students and postdocs in my lab were figuring out what was needed to be done differently with human tissue.”

For one thing, the sheer amount of tissue that would be removed from Spudich would be much larger than a tiny mouse lung. Furthermore, the researchers couldn’t use mouse-specific antibodies to separate the human tissue into specific cell types. And although some types of cells are relatively abundant and easy to analyze, others require meticulous care to isolate. “We’re not just interested in the tumor cells themselves,” Krasnow said. “We also want to understand the roles played by the cells that surround the tumor, the immune cells that have infiltrated the tumor and even the cells that form the vessels that deliver blood to the growing mass. Bulk analysis, in which several cell types are combined, obscures much of the most interesting information. We wanted to sample all major cell types in the tissue in and around the tumor, and in the healthy neighboring lung.”

MOVING QUICKLY

KRASNOW’S TEAM PULLED out all the stops to find the appropriate materials for the research.

“All of these people scurried about

until late in the night to scrounge reagents and antibodies from other labs, either here on campus or nearby,” Krasnow said. He also alerted Lisa Nichols, PhD, who directs the Beckman Fluorescence Activated Cell Sorting Facility, to prepare for an influx of samples. “We had to line up time on the cell-sorting machines and find FACS operators who could be on-call after the surgery,” Krasnow said. “And all of this had to be put in place by 8 a.m. the next morning.”

‘All of these people scurried about until late in the night to scrounge reagents and antibodies from other labs, either here on campus or nearby.’

In addition to facilitating the efforts of the rapid response team, Krasnow marshaled other lung adenocarcinoma researchers at Stanford.

“I was on the East Coast at a meeting that afternoon when I received a phone call from Mark,” Maximilian Diehn, MD, PhD, associate professor of radiation oncology, recalled.

“Would I be interested in collecting plasma for study?”

Diehn, who earned his doctorate in biophysics in the Department of Biochemistry at Stanford, is studying whether the presence and levels of circulating tumor DNA, or ctDNA, which is shed into the bloodstream by tumor cells, can be used to diagnose or to predict the recurrence of the disease after initial treatment. He and Ash Alizadeh, MD, PhD, associate professor of oncology, have shown that if ctDNA is detected after radiation and surgery, that patient is at high risk for recurrence.

“Jim’s cancer type and stage basically fit perfectly into one of our ongoing clinical studies,” Diehn said. “By collecting blood before and after surgery, and then intermittently during and after subsequent chemotherapy, we can look for the presence of ctDNA and possibly predict the chance of recurrence.”

Diehn and Alizadeh have also helped develop a test in Stanford’s Molecular

Pathology Laboratory to identify the presence of genetic changes in a tumor that can be targeted by existing drugs or treatments.

Krasnow still had a few more experts he wanted to involve.

“Immunotherapy is a very exciting field of research right now, and we wanted to reach out to experts of the immune and blood system to systematically analyze immune cells infiltrating Jim’s tumor,” Krasnow said. Irving Weissman, MD, director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine and of its Ludwig Center for Cancer Stem Cell Research and Medicine, fit the bill perfectly. He and Spudich are longtime friends.

Rahul Sinha, PhD, a former postdoctoral scholar in Weissman’s lab and an instructor at the institute, came on board to collect the necessary blood and tissue samples and initiate the analysis of tumor-infiltrating immune cells.

Finally, Krasnow called professor of medicine Calvin Kuo, MD, PhD, and hematology and oncology fellow Ameen Salahudeen, MD, PhD. Together with Tushar Desai, MD, associate professor of medicine, the two had been working to establish new ways to culture normal and cancerous human lung tissue from surgical biopsies to study human-specific biology.

“Again, we were just so fortunate to have world experts, or in many cases *the* world expert, right next door,” Krasnow said.

“Jim’s cancer is going to be one of the most heavily analyzed human cancers ever,” Diehn said.

‘A VERY BUSY PATIENT’

BY THE NEXT MORNING, SPUDICH was “a very busy patient,” signing multiple consent forms and being briefed on what his participation in each study entailed.

Jim's attitude was amazing," Krasnow said. "In everything he does, he has a wonderful blend of vision and hope. This was no different." Meanwhile, the rapid response team was gowned and waiting, somewhat nervously, outside an operating room at Stanford Hospital.

"These are PhD students and post-docs," Krasnow said. "I don't think any of them had ever been in an operating suite before, or even seen or touched fresh human tissue. But there they were, after being up much of the night, as Shrager removed the tissue through the tiniest of incisions."

Christin Kuo was in the operating room to discuss with Shrager and the pathologists how to get the best samples of normal and diseased tissue for the planned analysis. "These sections were precisely annotated and hand delivered to the lab immediately, to ensure the freshest tissues," Kuo said.

"From that point on, except for the size of the samples, it was pretty much like handling mouse tissue," Krasnow said. "Except this time it was someone they knew."

Under the care of Shrager and his team and Heather Wakelee, MD, professor of oncology and a specialist in lung cancer, Spudich recovered quickly from the surgery. "I was up and walking the halls that evening," he recalled. "I really can't say enough about Drs. Shrager and Wakelee and all the oncology care team at Stanford. They are phenomenal, and I am so thankful."

Because his cancer was caught early and removed fully, it's presumed to be cured. However, the current standard of care recommends several rounds of chemotherapy to reduce the chance of any possible recurrence. For patients with cancers that have spread to other parts of the body the prognosis is less positive.

"In metastatic disease, chemotherapy is used to prolong life rather than cure the patient," Wakelee said. However, new approaches include an immunotherapy approach, known as checkpoint blockade, and personalized treatment based on the genetic sequence of the tumor to more precisely target cancer cells.

"Previously, we would treat all metastatic lung adenocarcinomas the same, while now we look very closely at the cancer's molecular underpinnings," Wakelee said. "Now we wouldn't think of starting treatment without understanding the genetic changes present in each patient's cancer."

Wakelee is the principal investigator for a clinical trial testing the effect of checkpoint inhibitors — drugs that release the brakes on immune cells that can keep them from effectively targeting cancer cells — on the cure rates for people with early stage lung adenocarcinoma. Spudich has enrolled in the trial. After completing post-surgery chemotherapy, half the participants will receive the active drug and half will be part of a control group.

A FULL PARTICIPANT IN THE PROJECT

"It's so interesting to be the patient — I'm receiving chemo — but also to be a researcher deeply involved in the decision-making and data-analysis process. For example, I attend regular meetings of the team to decide what to do with the tissue samples," Spudich said.

"Jim's not just a patient, he's also a scientist," Krasnow said. "He started reading all our papers in the field. He wants to know everything. He quickly became not just a huge motivation for us all, both scientifically and personally, but a full participant in this project."

Raj Rohatgi, PhD, associate professor of biochemistry and of medicine and a close friend of Spudich's, facilitated Spudich's involvement in the scientific aspects of the work. "Raj is an expert in lung cancer and a close colleague of Heather Wakelee's," Spudich said. "He is extremely knowledgeable about the molecular and cell biology of the disease, and he's been invaluable to me. Mark, Raj and I confer almost daily about the latest developments in Project Lung."

In the months since the surgery, the scientists have amassed unprecedented amounts of data as a result of Spudich's impromptu visit to Krasnow's lab.

"Major results are starting to pour in," Krasnow said. "We've already learned that there are cell types in humans that

are either not present or not detectable in mice, which is very interesting. We've also identified a potential driver mutation for Jim's tumor."

Diehn and his colleagues have identified a genetic change in Spudich's cancer that, although relatively rare in lung adenocarcinoma, is common in melanoma. Drugs exist that target cancer cells with that mutation when the cancer is metastatic, but they are not yet approved for use in early stage cancers.

Krasnow and his colleagues are working to identify further subpopulations of cells in the lung. "We want to get to know the tumor and what is driving it," he said. "Are there subpopulations that might be responsible for maintaining and expanding the cancer?"

Previous work in Krasnow's lab has found that a small fraction of cells called alveolar type 2 cells can also act as stem cells to repair damaged tissue. To maintain their stem cell identity, the cells require the presence of neighboring cells called fibroblasts that secrete a signaling molecule called Wnt. "These alveolar type 2 cells are basically stem cells with a day job," Krasnow said, "and they have a private niche of just one adjacent fibroblast." If these stem cells are inappropriately activated, it's possible they could begin dividing uncontrollably and give rise to an adenocarcinoma, the researchers believe.

"We really want to know what goes on in the very earliest stages of cancer development," Krasnow said. "Are there any signs that it initiates in these alveolar type 2 cells? Intriguingly, it turns out that Jim's tumor DNA does have a cancer-associated mutation in one of these activating pathways. And now we have the opportunity to study them at single-cell resolution and compare them much more carefully to normal lung cells."

POTENTIAL APPROACH FOR CURE

One concept Krasnow and his collaborators are pondering is the idea that it might be possible to cure, rather than treat, lung cancers with a two-pronged approach: blocking the pathway that stimulates the cells' growth while re-

moving the Wnt signal that is necessary to confer the cells' stem cell properties.

"This is a foundational study," Krasnow said. "We've marshaled numerous experts and techniques in an effort to truly understand for the first time the full cellular and molecular complexity of a single tumor in a way that will push us to a whole new level of potential therapies for this disease."

"It's so amazing what you can do in 2018," Spudich said. "A lot of these techniques were invented right here at Stanford, many in the Biochemistry Department in which I spent so much of my career. If someone asks me exactly what we're going to learn from this study, I would answer the same way I answered when people asked me what would come out of Bio-X when it was first proposed. 'If I could tell you that, then we have failed.' But it's very exciting to imagine that I have a chance to help unravel what causes these cancers in the first place and the molecular details that might lead to new treatments." **SM**

— Contact Krista Conger at kristac@stanford.edu

FEATURE

Compassionate intelligence

CONTINUED FROM PAGE 15

evaluate cardiovascular event risk, leading to flawed clinical recommendations for nonwhite populations.

"If we feed racially or socioeconomically biased data into our algorithms, the AI will learn those biases," said Char.

HUMANITY AT THE END OF LIFE

Harman now uses the second generation of Shah's palliative prediction tool. Each morning, it emails her a list of newly admitted hospital patients who have a 90 percent or higher probability of dying in three to 12 months. There are no names on the email or details about why they're on the list. It's up to Harman to review the medical records she receives and decide if those patients have palliative care needs. She's found the list to be helpful, and she sees how it can improve hospital care and enable her to spend more time with the most critical patients.

"Human physicians are way better at

predicting death within a few days, but I'd bet on my model over a physician any day in predicting death three to 12 months out," Shah said.

The algorithm design and preliminary results of the first pilot study were published online in *arXiv* on Nov. 17, and another Bay Area health-care institution will be soon piloting the algorithm.

"This isn't a population of patients with a single disease or more predictable courses of illness," said Harman. "The patient might have five or 10 different problems that are all interacting with one another — not just a stroke, but also cancer and emphysema, for example. With this model, it looks over a longer time frame, analyzing the overall trajectory of this patient, not just what is happening during this hospital visit."

The palliative care staff still acts on clinician referrals in their daily rounds, but this model provides Harman with longer-range projections on people who might have been overlooked. On a typical day, she meets with the primary care team regarding two to three patients on the model's list. The cases that Harman selects are reported back to Shah's group so that they can monitor the algorithm's selection accuracy over time.

Harman has become attuned to the physical signs that a person is about to die. Breathing becomes irregular, with longer and longer pauses, the jaw dropping open with each breath. As the heart weakens, hands, feet and knees become mottled and cool to the touch. And there's the most profound moment, when there is only stillness. As a patient takes the last breath, Harman has her own ritual to usher them to the other side.

"I always say goodbye and thank you — sometimes out loud, sometimes not. I touch them, usually their hand or foot. I talk with the families. Sometimes they tell stories about the patient — usually funny ones. And I sit and listen for a spell. Even in the midst of such loss, families are welcoming. I express my sorrow for their loved one's death, though not always in words. I don't consider this the end; I believe that all of their souls carry on." **SM**

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FEATURE

A global vision

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where people binge-watch the content because it's so engaging and they want to share it with their friends," she said.

Digital MEDIC South Africa launched its 100 Percent Breastfed campaign earlier this year with a two-minute video featuring three South African celebrities who are mothers. Each of them calls breastfeeding "the first choice for feeding my baby." The campaign also includes a website with 27 videos in English and Xhosa on such breastfeeding topics as how breastfeeding works, its benefits, unsafe practices, and breastfeeding and HIV.

"I don't think we're done yet," said Adam, noting that she anticipates refining the videos further and creating more on new topics, all of which can be used in South Africa and beyond. "We need to have a comprehensive global library of content that is uplifting, empowering and evidence-based."

SEEING RESULTS IN CAMBODIA

Stanford Medicine's bid to impact 2 billion lives involves leveraging existing projects to launch new ones, and the effort to develop prehospital systems has gone to many other countries beyond India. Stanford Emergency Medicine International, a section in the Department of Emergency Medicine, has drawn on its experience with GVK EMRI to design and support prehospital training courses for Cambodia, the Middle East and Bhutan.

Stanford emergency medicine physicians hope the Nepalese government, which is looking to foster nationwide ambulance service, chooses to support NAS in much the same way that government leaders in India chose to help fund GVK EMRI's expansion into 15 states and two territories. "In EMRI's case, government officials became believers after witnessing the positive impact of the nascent EMS system on morbidity and mortality," according to a paper by several members of Stanford's emergency medicine faculty.

The lessons are also influencing Cambodia, where Stanford Emergency Medicine

International, the government Ministry of Health and the University Research Consortium are being funded by USAID for a five-year project to reduce maternal, infant and child death. Cambodia lacked an organized prehospital system for these cases: Transfers from one facility to another were done on an ad hoc basis; triage was not based on need but rather on first come, first served; and there was no common set of guidelines for emergency care, said Peter Acker, MD, an assistant professor of emergency medicine who has worked on the Cambodia initiative, as well as in Nepal and India.

The project has brought triage and referral systems to 38 hospitals in nine of Cambodia's 24 provinces, and educated providers about emergency protocols, record-keeping and using ambulances. Acker shared a recent report from one of his colleagues to USAID showing how these factors converged to make a difference in one case. A young woman came in the evening to a small rural hospital after delivering her child at home a few days earlier. "She had retained products of conception" — likely remnants of her placenta — "which was leading to severe postpartum hemorrhage," he said.

Whereas once she likely would have waited her turn, the staff quickly identified how seriously ill she was. "They were able to begin therapy immediately based on new guidelines," Acker said. They then used a hotline that had been set up for urgent conversations with staff at larger facilities. Upon learning of the case, a hospital with a blood bank and an operating theater sent an ambulance to pick her up. She arrived with her records and immediately had surgery to remove the material from her uterus.

"She is doing great," said Acker. "Knowing what was in place before, I think I can say she would have passed away without these changes."

It's one more life that Stanford Medicine has touched. **SM**

— Contact Jonathan Rabinovitz at medmag@stanford.edu

FEATURE

The doctor is in ... your gut

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methodical way to optimize it to improve efficacy.

This problem plagues animal research, too. "You can show that a mouse's outwardly observable characteristics change — for instance, it puts on weight, or sheds it — when you alter its gut-microbial contents via a fecal transplant. But now you're stuck: Which specific bug in that transplanted microbiota was responsible? You have no idea. From that point it's impossible to do anything more, because the fecal transplant isn't defined."

Then there's the scale-up problem. It's hard enough to find donors who have specific metabolic attributes you desire. But even if you've demonstrated that a particular human donor's microbiota is adept at, say, reversing obesity or eliminating insulin resistance, you can't treat an unlimited number of patients from one donor. And without knowing exactly what's in there and how these component strains are interacting, you can't just cook up huge quantities of it.

So Fischbach, Sonnenburg, Dodd, Huang and others are fashioning a work-around: a defined "model microbiota" to serve as a scaffold for purposed, customized designer microbial communities.

"Why not just completely replace somebody's gut microbes with a community that's built to spec?" Fischbach said.

You can generate such a defined "alpha-template" from the bottom up or from the top down, said Huang. "There are two complementary views on any engineering problem," he said. "You can try to build a radio from components you understand. Or you can take the radio out of a car and try to figure out how it works."

Fischbach and Sonnenburg are proceeding from the bottom up. "We're assembling an entire gut community from scratch," Fischbach said. "Something

like 100 or 200 microbial strains are shared by pretty much every person's gut. So we're starting with them. We're using them as a scaffold — putting those roughly 100 or so strains into germ-free mice, letting them get comfortable, then challenging that community by introducing a complete fecal sample from humans and seeing which new strains manage to get a toehold. Every new member must be filling some not-fully-exploited niche in this ecosystem. We sequence the newcomers, find out who they are, add them to the community and do the same thing again, repeating until things get reasonably stable — the rate of strain gain and loss bottoms out."

Huang is taking the top-down approach: suspending mouse fecal pellets in test-tube environments resembling that of the gut. He's also seeing what changes occur when you systematically vary the culture medium (by, say, denying them a certain nutrient or by giving them more of it) or subtract one resident strain at a time. The idea is to generate a reduced, but stable, complex microbial community of 100 species or so whose metabolic characteristics are well understood.

Either way, once the researchers can derive a defined, stable, scalable scaffold, they can alter one bug at a time to build customized, synthetic, side-effect-free gut communities that predictably produce, or don't produce, specific chemicals and can survive and thrive in a real human intestine.

'WE'RE ASSEMBLING AN ENTIRE GUT COMMUNITY FROM SCRATCH. SOMETHING LIKE 100 OR 200 MICROBIAL STRAINS ARE SHARED BY PRETTY MUCH EVERY PERSON'S GUT. SO WE'RE STARTING WITH THEM.'

"We don't need to build custom communities for every person," Fischbach said. "We could build one community for, say liver disease and another for inflammatory bowel disease or chronic kidney disease, analogous to different drugs that each treat these separate conditions in lots of people. One therapy can work in hundreds of thousands of people."

But the one-step-beyond "abdominal medicine

cabinet” is still many years away. The advent of a purposed, customized designer microbiota will have to await the patient collection of dozens or hundreds of “pill bottles” — the discovery and/or manipulation of individual gut microbes, or specific genes in a microbe, that can make a sustainable contribution to human health.

“We’re not very far along yet,” said Fischbach. “We’re making demonstrable progress, though. We’ve reached the jumping-off point.” **SM**

— *Contact Bruce Goldman at goldmanb@stanford.edu*

FEATURE

Sparking drug discoveries

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to ascertain market size and carefully choose an indication for the drug. And think about how VCs and big pharma will view it, and regulatory organizations too. That’s all very different from research.”

Back at her university, the team completed more research, had more meetings with advisers and Tseng practiced her pitching. “The more you talk with other people in SPARK, the more you understand, the better your project becomes,” she said.

The team members’ goal is now clear: They are aiming to create a company, and additional research has uncovered more conditions the drug could treat. Initial clinical trials indicate it might also be a treatment for ataxia, a rare, debilitating neurological disease with no treatment, as well as early onset Alzheimer’s disease.

One of the participants in the clinical trials was a man with severe dementia. “He couldn’t use the phone anymore, he didn’t understand what the phone is about,” said Tseng. “Then he has six months on the high-dose arm of the trial and he’s happily calling his son every day. They were upset after the trial ended.

“You have a heart and scientific ability, but then you have to have the trained skills to bring that into a product. SPARK makes that possible.”

At the showcase the next year, she pitched with more confidence. She made progress fundraising and afterward she spent time at Stanford to connect with SPARK’s Stanford network of advisers and meet physicians, such as autism expert Antonio Hardan, MD, professor of psychiatry and behavioral sciences.

So about testing her team’s compound as an autism treatment? Well, she was eight months pregnant when she met Hardan and she thinks that influenced her decision to take on the challenge. “When you are pregnant and people talk about autism, I think that it gives you courage.” The drug candidate is now in clinical trials for autism at Stanford and National Taiwan University Hospital in Taiwan.

“I can relate to those parents,” she said. “They would do anything to help those kids, and it made me want to, too.” **SM**

— *Contact Rosanne Spector at manisbma@stanford.edu*

FEATURE

Never give up

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Shefrin has allowed Kwong to take additional skin tissue for research analysis to better understand the disease and possibly develop targeted therapies. Gotlib said he plans to sequence the roughly 23,000 genes in normal and abnormal tissues that encode for proteins, using samples from Shefrin and other patients, in a search for a mutation that might be the source of Schnitzler syndrome.

“We haven’t found the gene for this one yet. So it’s a fishing expedition,” he said.

Although Shefrin’s health will never be as good as it was before she developed Schnitzler, not a day goes by that she doesn’t think of and thank “my brilliant doctors,” Gotlib and Kwong, she said. She is back to sewing and knitting, playing bridge, walking her terrier, and socializing. She will need to inject anakinra every day for the rest of her life; fortunately, she has had few side effects. Without anakinra, the skin rash and severe

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joint pain return within hours. Because the medication suppresses her immune system, she takes precautions to protect against infection.

She said she decided to share her story in the hope of helping those who may have undiagnosed Schnitzler’s. “If just one person recognizes his or her symptoms in my illness and is able to get help, then having told my story will make it worthwhile.” **SM**

— *Contact Ruthann Richter at medmag@stanford.edu*

PERFECT PAIRING

TECHNIQUE COULD EASE A PROMISING CANCER THERAPY'S SIDE EFFECTS

Scientists frustrated by the nasty side effects of a promising immune therapy that effectively kills cancer cells have found a way to keep the therapy working longer while eliminating the devastating reactions. If the new technique is proven to be as successful in humans as it was in mice, scientists want to incorporate it into the therapy, called adoptive cell transfer.

The therapy takes advantage of a patient's natural immune system by using a patient's own blood; purifying it; and extracting immune cells, called killer T cells, which are designed to destroy foreign intruder cells. Scientists then genetically alter those cells — to make them especially adept at finding and destroying specific cancer cells — and inject them back into the patient's circulatory system.



To succeed, T cells need nudges from a protein called interleukin-2, which binds to receptors on the surface of T cells. When faced with such biological threats as bacteria or viruses, our bodies secrete the IL-2 protein, whose job is to activate T cells.

"These bioengineered T cells need IL-2 to survive, to work and to expand in number, just as our natural ones do," said Christopher Garcia, PhD, professor of molecular and cellular physiology and of structural biology, and senior author of a study about the technique published March 2 in *Science*.

But nature doesn't produce enough IL-2 to keep altered T cells revved up, so they fade and burn out, Garcia said. To keep modified T cells active, patients must be injected with IL-2 "booster shots." Huge doses of the powerful protein, however, have nasty side effects that can outweigh treatment benefits. They include weight loss, restricted mobility, hypothermia, and enlarged spleen and lymph glands. It also can cause inflammation in cells that are better left alone during cancer treatment. Some patients also experience pulmonary edema, in which their lung tissue fills up with fluid, making it difficult or impossible for them to breathe.

Garcia and his team created a workaround by engineering new versions of both IL-2 and its corresponding receptor that bind only to each other. This keeps cancer-targeting T cells working without causing side effects by activating other T cells, he said.

Garcia credited Jonathan Sockolosky, PhD, lead author of the study and former postdoctoral scholar, with pairing up the modified protein and receptor. In the lab, Garcia's group snapped modified receptors onto T cells from mice and showed that these T cells responded to modified IL-2 exactly as natural T cells would be expected to respond to ordinary IL-2. Then, in tests in mice, collaborators from UCLA and UCSF shrank tumors using bioengineered T cells that had been outfitted with modified proteins and receptors, with none of the side effects that come from natural IL-2 infusions.

"Adoptive cell therapy is on the cusp of becoming a revolutionary new approach to cancer treatment," Garcia said. "It's undergoing explosive growth — it's a multibillion-dollar biotechnology industry already, and it's going to become as routine as bone marrow transplants are now. But all of the approaches in development today need IL-2, so new and better ways of delivering IL-2 are a critical unmet need." — BRUCE GOLDMAN

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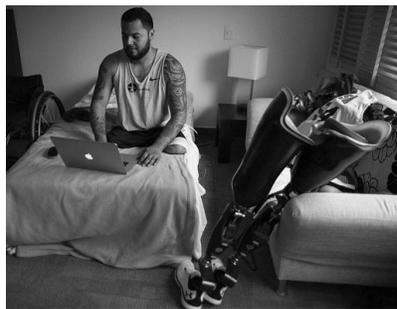
TEAMS COMPETE TO DESIGN AN ALGORITHM THAT CAN HELP PEOPLE WITH PROSTHETICS MOVE

Designing a computer model of a virtual person learning to walk is a little like a baby learning to walk: There's a lot of falling down. The difference is that, unlike a baby, a virtual person doesn't have a brain to guide the process of moving muscles, bones and joints to ensure that upright movement is possible. Still, Stanford researcher Lukasz Kidzinski, PhD, is optimistic that, through crowdsourcing, it's possible to help living, breathing humans by creating algorithms that can simulate the movements of the limbs of virtual people. Last year, Kidzinski, a postdoctoral scholar in bioengineering, created a contest that enticed 442 teams of academics, private-sector artificial intelligence researchers and enthusiasts from around the world to design algorithms to teach virtual musculoskeletal models of athletes how to walk, run and eventually navigate an obstacle course.

Contestants used highly accurate computer models of musculoskeletal structures that were created by Kidzinski's adviser, Scott Delp, PhD, professor of bioengineering and of mechanical engineering. His models are widely used for surgical navigation.

This year, teams are working with a virtual body that includes a prosthetic leg. The aim is to guide research into better prosthetic designs and to determine the best approaches for helping people learn to move with them.

"Last year was more of a proof of concept," Kidzinski said. "This year we want to get closer to medical applications."



A STANFORD RESEARCHER'S PROJECT TAPS INTO CROWDSOURCING TO HELP PEOPLE WITH PROSTHETICS.

More than 250 teams have signed up. They are judged on how far their virtual competitors can walk from a starting point. No one has succeeded in designing a model that can walk with a prosthetic leg, but Kidzinski said that by this time last year, no team had managed more than a few steps. Some fell flat on their faces, virtually speaking.

The fact that last year's winner made it through an obstacle course showed that the approach could work.

"Compared with the first challenge, this new challenge is a big step forward," Kidzinski said.

Nvidia will award graphics-processing units to the top three teams, and Google has offered cloud computing resources for teams who might otherwise find it difficult to take part.

Details about NIPS 2018: AI for Prosthetics Challenge are available at <https://stanford/2Zg8yRF>. The deadline to enter is Sept. 15. — NATHAN COLLINS

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