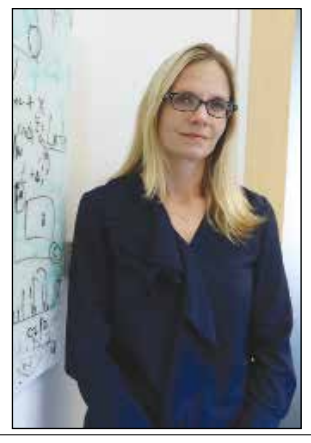
INSIDE STANFORD MEDICINE

Volume 10, No. 10 ■ May 21, 2018 ■ Published by the Office of Communication & Public Affairs



The Precision Health and Integrated Diagnostics Center aims to prevent healthy people from becoming ill.

Page 4

Multigene tests for breast cancer on the rise

By Krista Conger

STEVE FISCH

"In general, multigene panel tests yield more clinically useful results and are rapidly becoming the norm," Allison Kurian said.

The use of genetic tests aimed at detecting the presence of mutations in the BRCA1 and BRCA2 genes in women with breast cancer is rapidly declining in favor of tests that can detect multiple cancer-associated mutations, according to researchers at the School of Medicine and five other U.S. medical centers.

Some researchers had wondered whether multigene testing, which may identify genetic mutations of uncertain clinical significance, would lead more women to consider prophylactic mastectomies — a surgery in which both breasts are removed to prevent future cancers — out of an abundance of caution. However, the current study did not show an increase in mastectomies associated with testing more genes.

The shift reflects a growing acknowledgement by clinicians that multigene panel tests can yield more clinically useful information for patients and their unaffected relatives, the researchers said.

Overall, multigene panels were about twice as likely as the tests for BRCA1 and BRCA2 to identify disease-associated genetic variants, the study found. However, multigene testing was more likely than the BRCA-only testing to be delayed until after surgery to remove the tumor. This time lag may limit a patient's treatment options, the researchers said.

'Becoming the norm'

"In general, multigene panel tests yield more clinically useful results and are rapidly becoming the norm," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "Newly diagnosed women should ask their doctors whether they may be appropriate candidates for genetic testing. They should also advocate for the opportunity to discuss genetic testing and its implications with an experienced clinician, such as a genetic counselor, in a timely manner."

A paper describing the research was published May 10 in *JAMA Oncology*. Kurian is the lead author. Steven Katz, MD, MPH, professor of medicine and of health management and policy at the University of Michigan, is the senior author.

Multigene panel tests are more likely than BRCA-only tests to yield information about both a patient and her family members, who may be unwitting carriers of disease-associated mutations. "This is very important because it offers the opportunity for genetically targeted, primary cancer prevention in unaffected relatives," Kurian said. "Some prior research has shown that this 'cascade testing' of unaffected relatives is cost-effective, and there are currently several initiatives underway to improve upon the delivery and success rates of cascade testing."

The researchers surveyed over 5,000 women who had been diagnosed with stage-0 to stage-2 breast cancer between 2013 and 2015. They asked the women if they'd had genetic testing, and, if so, who ordered it, when it was performed and what type of tests they underwent. A novel feature of this study was that genetic results came directly from the testing laboratories and were linked to population-based cancer registry data. This data linkage provided substantially greater depth and accuracy of genetic information than in previous studies.

They found that only about one-quarter of the women had received any genetic testing. This number stayed relatively constant throughout the two-year period. However, of those who were tested, the proportion who received multigene panel testing increased steadily over time, from about See MULTIGENE, page 7

Scientists manipulate gut bacteria in mice using a type of seaweed

By Krista Conger

Gut bacteria thrive on the food we eat. In turn, they provide essential nutrients that keep us healthy, repel pathogens and even help guide our immune responses.

Justin Sonnenburg

Understanding how and why some bacterial strains we ingest can successfully take up residence in the large intestine, while others are quickly evicted, could help scientists learn how to manipulate the makeup of thousands of bacterial species there in ways that enhance our health or help fend off disease. But the sheer complexity of gut ecology has hampered this task.

Now, researchers at the School of Medicine, working with laboratory mice, have shown that it's possible to favor the engraftment of one bacterial strain over others by manipulating the mice's diet. The researchers also have shown it's possible to control how much a bacterium grows in the intestine by calibrating the amount of a specific carbohydrate in each mouse's water or food.

"We're all endowed with a microbial community in our guts that assembled in a chaotic manner during our first few years of life," said Justin Sonnenburg, PhD, associate professor of microbiology and immunology. "Although we continue to acquire new strains throughout life, this acquisition is a poorly orchestrated and not-well-understood process. This study suggests it could be possible to reshape our microbiome in a deliberate manner to enhance health and fight disease."

A paper describing the research was published online May 9 in *Nature*. Sonnenburg is the senior author. Former graduate student Elizabeth Shepherd, PhD, is the lead author.

Giving bacterium a leg up

The burgeoning field of probiotics — live, See SEAWEED, page 7

PET scan tracer predicts success of cancer 'vaccine,' study reports

By Hanae Armitage

By engineering a special molecule to track certain immune cells in the body, scientists at the School of Medicine have invented a litmus test for the effectiveness of a newly devised cancer therapy.

Sam Gambhir

The molecule is a radioactive tracer that latches onto immune cells when they're activated — the status that immune cells, in particular T cells, assume when they're poised to kill tumor cells.

"It's not good enough to just image all T cells; you need to image activated T cells because those are the ones that are going to kill the tumor," said Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology at Stanford. "The problem that occurs in other approaches, including ones we've previously developed, is that they're sometimes not specific enough. I could image tumor patients who've yet to receive an immunotherapy; they'll sometimes show T cells in their tumors, but those T cells aren't always activated and killing tumor cells — so we need a way to track activated T cells more specifically, and I think we've done that here."

With the tracer, doctors can theoretically see if a cancer vaccine has successfully galvanized T cells into a protective state, though the research conducted in this study was exclusively in mice. The PET tracer's capabilities aren't limited to cancer therapies, Gambhir added. Because the tracer latches onto a molecule that flags any activated T cell, it also makes for a powerful tool to detect autoimmune diseases, which occur when the immune system erroneously activates T cells to attack healthy tissue.

A study describing the tracer was published online May 14 in the *Journal of Clinical Investigation*. Postdoctoral scholar Israt Alam, PhD, and graduate student Aaron Mayer share lead authorship of the See TRACER, page 7

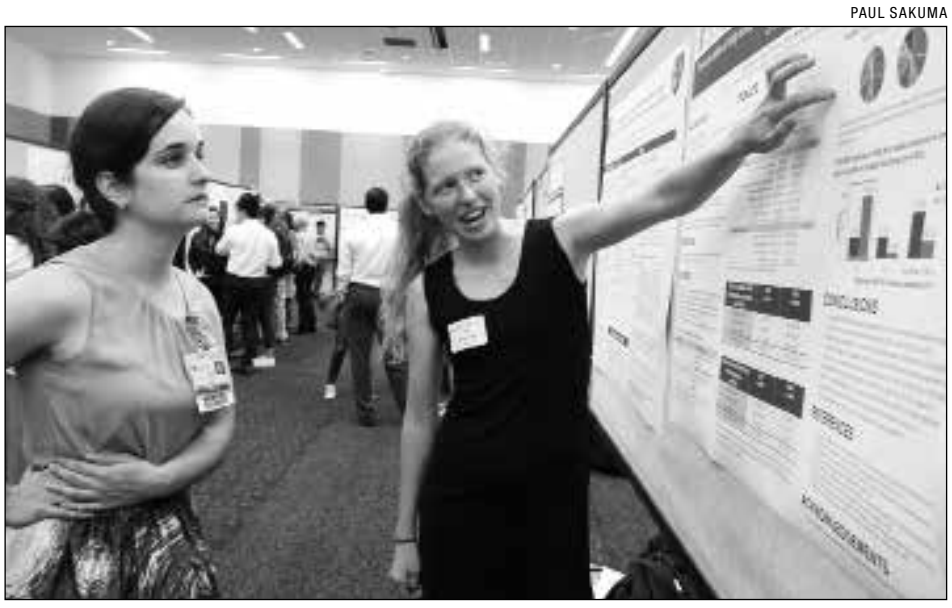
Student research symposium showcases curiosity and scholarship

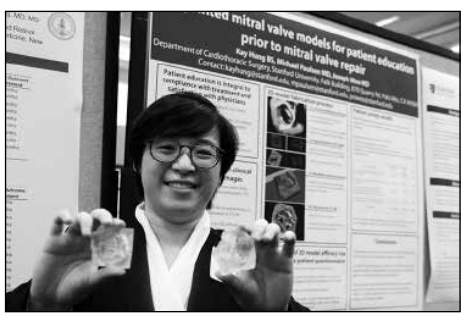
By Julie Greicius

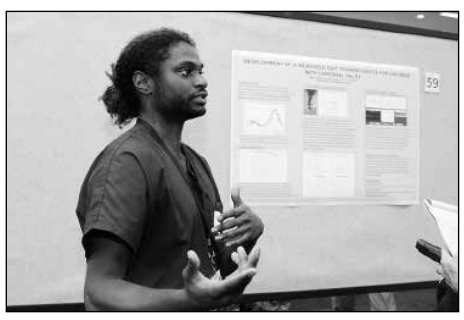
In his last year as an undergraduate student in bioengineering at Washington University in St. Louis, Missouri, Sheun Aluko took a contemporary dance class and two yoga classes. Inspired by the intersection of movement and bioengineering, Aluko was drawn to the possibility that technology could provide real-time feedback for physical therapy.

On May 16, at the 35th Annual Stanford Medical Student Research Symposium, Aluko, now a third-year medical student at Stanford, discussed his research project, "Development of a wearable gait-training device for children with cerebral palsy." He is conducting the research under the guidance of a faculty mentor, Jessica Rose, PhD, professor of orthopaedic surgery and director of the Motion & Gait Analysis Laboratory at Lucile Packard Children's Hospital Stanford.

PAUL SAKUMA







(Clockwise from top) Medical student Katherine Dickerson listened to fellow student Brigit Noon discuss her poster presentation May 16 at the 35th Annual Stanford Medical Student Research Symposium. Sheun Aluko discussed his project, "Development of a wearable gait-training device for children with cerebral palsy." Another presenter, Kay Hung, is investigating the feasibility of producing flexible, 3D-printed models of the mitral valve for patient education prior to mitral valve repair.

Aluko was one of 64 medical students who presented posters of their research projects to a roomful of their peers, faculty, staff and others at the symposium in Berg Hall at the Li Ka Shing Center for Learning and Knowledge. Forty-eight faculty and staff members served as judges. They circulated, asking questions of the presenters and taking notes.

"This symposium is the one yearly session where the students are the focus," said Neil Gesundheit, MD, MPH, interim senior associate dean for medical education and professor of medicine. "Their projects reflect close collaborations between our students and our faculty, because typically on each poster the student is first author, and the faculty mentor and sponsor of the work is senior author."

'At the edges of science'

This year's posters represented just a sampling of work by Stanford's medical students, many of whom present their research at other national and international conferences instead of, or in addition to, presenting at the symposium. Their research interests span an enormous range.

"Our students are constantly interested in being at the edges of science and finding opportunities to get into those labs and do things, which I think is super exciting," said Laurence Baker, PhD, director of the Scholarly Concentration Program and professor of health research and policy.

Brigit Noon, a second-year medical student, spent a quarter devoted to research on a retrospective analysis of data showing trends in the uptake of long-acting, reversible contraceptive methods — such as intrauterine devices or contraceptive implants — for women in the immediate postpartum period.

"This project was particularly interesting to me because it focuses on a forgotten population of women who are actually very highly susceptible to becoming unintentionally pregnant after delivering a baby," Noon said. "That's driven from perhaps lack of knowledge, a belief that you can't get pregnant when you're breastfeeding, or other ideas about suppressed fertility."

Most student research is financially supported by the Medical Scholars Research Program, a grant program that has been active at Stanford for nearly 40 years. "Altogether, we fund something on the order of 200 quarters of research by medical students each year," Gesundheit said. "That's in addition to other sources of funding. And that's what makes it remarkable."

Generous financial support is just part of what makes Stanford medical students' research projects happen. "Stanford has a long history of being a real leader in this area, working very hard to make it possible for students not just to get money from the grant program, but to have entrée to faculty projects and activities," Baker said.

> "We fund something on the order of 200 quarters of research by medical students each year."

For faculty mentors like Baker, who has overseen the symposium for 10 years, supporting students is uniquely rewarding. "We see students who come here without a lot of research experience sometimes, but who really find a passion area," Baker said. "We also have students who achieve at high levels, so the idea that we can help them get their papers into *Science* or *Nature*, or work with people to create what may ultimately become major projects for them in their careers, I just think that's super cool."

Kay Hung, a second-year medical student, investigated the feasibility of producing flexible, 3-D-printed models of the mitral valve for patient education prior to mitral valve repair, then measured the improvements in patient understanding and satisfaction, as compared with those who received traditional education before their procedure. She said her faculty mentor, Joseph Woo, MD, the Norman E. Shumway Professor and professor of cardiothoracic surgery, was encouraging.

"He always asked questions I hadn't thought about, and got me thinking in new directions, especially when I was stuck," Hung said. "But he never did the work for me, and I really appreciated that."

The scholarly concentration has been a requirement for medical students at Stanford since 2003. Many students say they are grateful for the way their research efforts help them develop connections with their peers, faculty members, graduate students and postdoctoral scholars, Baker said.

"Often enough, someone will say, 'I wouldn't have done this project, but I had to. Then I found a group of people I like, and I found a mentor I can work with, and an area of research I'm really into,'" Baker said. "You meet people and you find things and they become part of your world in a new and possibly expanding way. And that's also an exciting thing for me to see."

"Just seeing and helping Stanford bring to bear what it can do for students is rewarding," Baker said, "because of the way the students use it and run with it, and because of the things they can do when they get these chances."

Winning poster presentations:

- Alvaro Amorin, "Stereotactic radiosurgery in the multimodal management of pituitary adenomas: a single center's experience." Mentor: Justin Moore, MD, PhD, surgical neuro-oncology skull base fellow.
- Jacqueline Aredo, "Impact of concurrent genetic mutations on KRAS-mutant non-small cell lung cancer outcomes and tumor PD-L1 expression." Mentor: Heather Wakelee, MD, professor of oncology.
- Henry Bair, "Patterns and factors associated with inappropriate antibiotic prescription for respiratory tract infections: a systemic review at Stanford Express Care." Mentor: Marisa Holubar, MD, clinical assistant professor of infectious diseases.
- Anita Chanana, "Targeting CCR1 expression in epithelial ovarian cancer." Mentor: Oliver Dorigo, MD, PhD, associate professor of obstetrics and gynecology.
- Jaclyn Konopka, "The influence of oral contraceptive hormones on anterior cruciate ligament strength." Mentor: Jason Dragoo, MD, associate professor of orthopaedic surgery.
- Anusha Kumar, "Interim findings from an open label phase 1B investigator-initiated study of Secukinumab in patients with moderate to severe papulopustular rosacea." Mentor: Anne Chang, MD, associate professor of dermatology.
- Jeffrey Kwong, "Assessing the Fisher, Millard, and Mohler techniques of cleft lip repair surgery with eye-tracking technology." Mentor: Rahim Nazerali, MD, clinical assistant professor of plastic and reconstructive surgery.
- George Liu, "Thyroid cancer risk in airline cockpit and cabin crew: a meta-analysis." Mentor: Chris Holsinger, MD, professor of otolaryngology-head and neck surgery.
- Julia Ransohoff, "Discovery of differential RNA binding and regulation by the APOL4 protein to disease-linked psoriasis CDSN gene variants." Mentor: Paul Khavari, MD, PhD, the Carl J. Herzog Professor in Dermatology in the School of Medicine.
- Megan Roche, "A prospective multicenter study optimizing bone health and preventing bone stress injuries in Division 1 distance runners." Mentor: Michael Fredericson, MD, professor of orthopaedic surgery. ISM

INSIDE STANFORD MEDICINE

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

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

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

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

STANFORD MEDICINE

Memorial service for Gerald Reaven is set for May 24

Memorial services will be held for Gerald "Jerry" Reaven, MD, professor emeritus of medicine, from 4-7 p.m. May 24 in McCaw Hall at the Arrillaga Alumni Center.

Reaven, whose decades of research at Stanford as an endocrinologist helped show that insulin resistance could lead to Type 2 diabetes and multiple other diseases, died Feb. 12. He was 89.

The program will begin at about 4:15 p.m., followed by a reception at the Ford Alumni Gardens. Speakers will include faculty, colleagues and members of the family.

In lieu of flowers, a memorial donation may be made to support "The Gerald M. Reaven Memorial Education and Research Fund" at https://makeagift.stanford.edu.

Checks may be made payable to Stanford University and sent to Stanford University Development Services, PO Box 20466, Stanford, CA, 94309-0466. Please note online or in the memo of the check: "In memory of Dr. Gerald Reaven." ISM

Reducing tapeworm infection could help academic performance

By Rob Jordan

A Stanford-led study in China has revealed for the first time high levels of a potentially fatal tapeworm infection among school-age children. The researchers suggest solutions that could reduce infections in this sensitive age range and possibly improve education outcomes and reduce poverty.

"This disease invades the brain," said John Openshaw, MD, the study's lead author and an infectious disease instructor at the School of Medicine. "Children who are affected during formative school years risk cognitive deficits which could enforce a cycle of poverty."

The study, published online May 8 in *PLoS Neglected Tropical Diseases*, focuses on *Taenia solium*, a tapeworm that infects millions of impoverished people worldwide and can cause a disorder of the central nervous system called neurocysticercosis. The World Health Organization estimates that the infection is one of the leading causes of epilepsy in the developing world and results in 29 percent of epilepsy cases in endemic areas. It is thought to affect about 7 million people in China alone.

"While historically researchers have studied adults with this disease, the burden on kids and what that burden means for affected countries in terms of lost productivity and lost income is unknown," Openshaw said. "We hope our work will fuel interest in figuring that out."

The study's senior author is Stephen Luby, MD, professor of medicine and senior fellow at the Stanford Woods Institute for the Environment and the Freeman Spogli Institute for International Studies.

JOHN OPENSHAW

Researchers are working to improve hygiene practices at schools in China's Sichuan province to help prevent tapeworm infection in children.

A global scourge

Found commonly in the muscle of pigs allowed to roam and consume human feces in regions without indoor toilets, the tapeworm can infest the intestines of people who consume under-cooked pork. Thousands of tapeworm eggs are then shed in the infected person's feces, contaminating the environment, including drinking water sources and food crops fertilized with human feces.

The disease can take a tragic turn when people directly consume the tapeworm eggs, either through contact with a person who has the eggs on their hands and clothing or by eating food contaminated with the eggs. In those cases, the tapeworm migrates out of the human digestive tract and can invade the brain. Symptoms of this infection can range from chronic headaches to seizures to psychiatric disturbances, such as hallucinations.

Schools as infection points

To explore whether children are particularly at risk of tapeworm infection, the researchers tested fifth- and sixth-grade students, mostly 11- to 13-year-olds, in a remote Himalayan region of western Sichuan province. The majority of the children boarded at their schools during the week. The researchers found antibodies for neurocysticercosis in as many as 22 percent of the children they tested in some schools — a rate that's higher than what the group saw in adults in surrounding villages.

> "The tools to eradicate this disease are available."

Openshaw said that the brain form of this disease spreads human to human, with no pigs required. "All you need is a couple people with gastrointestinal tapeworms and poor hygiene," he said, conditions that exist in rural schools.

Unlocking a solution

Many of the children have only one or two pairs of clothes at school, so they wear and sleep — sometimes in shared beds — in the same set of clothes for days at a time. Attempts to have the children wash their clothes are infrequent and of mixed success, according to Openshaw. School bathrooms are generally unhygienic pit latrines, soap is rarely available and taps for hand-washing don't work in many cases.

"Schools appear to be hotbeds of transmission, as well as places for potentially effective intervention," Openshaw said.

Community education will be key to pushing down infections: A third of parents who responded to a survey believed intestinal worms have no adverse effects, and 19 percent thought less activity and drinking hot water or eating spicy food would help.

The researchers also plan to distribute medication in schools to counter the tapeworms and administer vaccines and anti-parasitic medications to pigs in the region. One such drug is particularly promising, according to co-author Stephen Felt, DVM, MPH, associate professor of comparative medicine. The drug, oxfendazole, not only kills muscle-encysted larvae in pigs, but protects them from reinfection for up to three months. Felt cautioned that oxfendazole may lead to unsightly scarring of the meat, which might turn off consumers. A vaccine called Cysvax also appears to be highly effective, but it requires booster doses — a significant drawback. Combining Cysvax and oxfendazole might be the most effective approach, according to Felt.

In schools, Openshaw and his colleagues are working to install working hand-washing stations near bathrooms, develop cost-effective ways of supplying soap, provide curriculum materials about the disease and hand-washing, and integrate good hand hygiene into school-based reward systems.

The researchers have forthcoming work that measures cognitive deficiencies in the children, and better defines social links — likely transmission pathways — among them.

"The tools to eradicate this disease are available," Openshaw said. "We hope that as the true burden of this disease on children becomes clearer, governments and nongovernmental actors will commit more resources."

Openshaw is also a faculty fellow at Stanford's Center for Innovation in Global Health.

Other Stanford co-authors are Alexis Medina, project manager for health and nutrition at Stanford's Rural Education Action Program; and Scott Rozelle, PhD, the Helen C. Farnsworth Professor in International Agricultural Policy and a senior fellow at the Stanford Institute for Economic Policy Research.

Researchers from Sichuan Centers for Disease Control and Prevention and Sichuan University also contributed to the study, which was funded by Stanford's Global Development and Poverty Initiative, the Burroughs Wellcome Fund and the American Society of Tropical Medicine and Hygiene.

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

At colloquium, a range of views on value of predictive algorithms

By Kris Newby

Is prediction enough?

This was the question animating a lively, debate-style colloquium — as well as the title of the event — April 25 on the promises and perils of machine learning. Organized by the Department of Health Research and Policy's Division of Epidemiology, some 200 data wranglers and scientists attended the event to hear an interdisciplinary lineup of speakers present their best arguments for and against various machine-learning strategies.

A video of this half-day event can be viewed at http://med.stanford.edu/epidemiology/causal_inference_colloquium.html.

Value of expert knowledge

Miguel Hernan, MD, DrPH, professor of epidemiology and biostatistics at the Harvard T.H. Chan School of Public Health, advocated for pairing algorithms with expert knowledge with. "For causal questions, we need data and a good algorithm, but we also need expert knowledge," Hernan said.

Nigam Shah, MBBS, PhD, associate professor of biomedical data science, described a project at the medical school called the "green button," which enables Stanford physicians to submit a clinical question to a bioinformaticist, then receive a quick-and-dirty answer in a few seconds, culled from 150 million patient records. He asserted that only a handful of these clinical questions could be answered with a medical guideline or a randomized clinical trial, so healthcare providers shouldn't let perfection be the enemy of the good; rather, physicians should be allowed to apply their expert knowledge to this kind of data-driven evidence to make the best clinical decisions.

The colloquium featured tales of investigators led astray by biased data, woefully misguided causal inferences and "black box" algorithms, so called because their decision-making processes are inscrutable to outside observers. Presentations included "Data science is science's second chance to get causal inference right: A taxonomy of data science tasks and its implications," "Avoiding discrimination through causal reasoning" and "Learning objectives for causal inference," "An informatics consult service for using aggregate patient data at the bedside" and "Offline policy evaluation for algorithmic decisions."

Michael Baiocchi, PhD, a statistician and assistant professor of medicine at the School of Medicine, issued a cri de coeur to attendees to not let algorithmic learning obliterate what we know about how to practice good science: "Being a statistician means we are defenders of the scientific method. We are the ones, through several generations, who have codified it, mathematized it and quantified it. We guide the content experts beyond the gate to help them find new knowledge and bring it back." **ISM**

STEVE CASTILLO

During a colloquium on machine learning on April 25 at the Clark Center, Miguel Hernan (far right), said, "For causal questions, we need data and a good algorithm, but we also need expert knowledge."

New center sets out to detect, stop disease before it starts

By Hanae Armitage

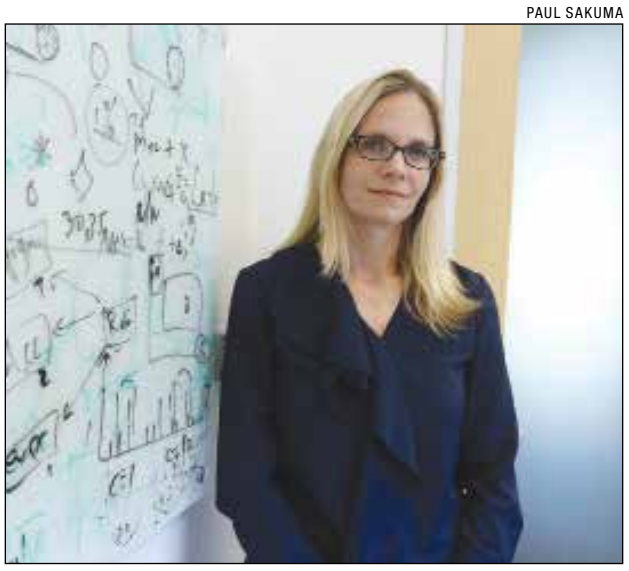
It's not often that world-class scientists band together to investigate disease with no intention of curing it. Yet upward of 55 scientists at Stanford's Precision Health and Integrated Diagnostics Center are doing just that in a push to get researchers and physicians off their heels and onto their toes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

STEVE FISCH

PAUL SAKUMA



Sam Gambhir is director of the Precision Health and Integrated Diagnostics Center. (Right) Christina Curtis, an associate member of the center, aims to create a blood test that can detect early on whether cancer is present and determine other complex information about it.

Officially established last year, the Precision Health and Integrated Diagnostics Center, abbreviated PHIND (and pronounced "find") now 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 at play here is one that grounds 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."

It's an effort that 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 in an effort 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." At PHIND, Snyder and a team of collaborators are putting various omics profiles to work in a clinical trial that aims to prevent Type 2 diabetes. ("Omics" more or less means "the study of" — so genomics would equate to "the study of genes," for instance.)

They're studying 100 people, all considered healthy but potentially prediabetic. All participants receive a device to track levels of glucose (sugar) in their blood in real time, around the clock. But there's more: Snyder and his group 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 for later examination.

The participants' glucose-tracking devices report levels of blood glucose throughout the day. Snyder is looking for "spikers": people whose glucose level skyrockets after eating carbohydrates. The sharp uptick in glucose indicates that something is askew with either their insulin — a hormone that helps the body turn carbohydrates into usable energy — or how the body takes up glucose, and it's a telltale sign of diabetes.

But as it turns out, 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, who is 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, the composition of their microbiome and their metabolome, and use this information to ideally piece together a diet plan that keeps their glucose levels under control."

The key here, 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."

Eventually, Snyder's goal is to compile all of this information — glucose readings, microbiome and metabolome profiles — and use machine-learning to not only predict who's at high risk for diabetes, but also to prescribe diets that harmonize with the needs of their metabolic tendencies to prevent the onset of diabetes.

"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 depression, suicide in teens

The beauty of precision health is that it can apply to nearly any field of biology, even the "squishier," harder-to-pin-down ones, like 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 (8-11 years old) into their early teenage years (13-16 years old). In the first leg of the study, scientists interviewed children and their parents about the children's stressful early life events — moving hometowns, 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.

Now, Gotlib and his team are continuing to follow these adolescents into their teen years and, with PHIND, they're not only able to keep measuring parameters from the first part of the study, but also buttress the data with new measures of inflammatory markers, high levels of which are often seen in depression.

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

Research from Curtis' lab shows that some cancers are simply born to be bad. That is, from day one, mutations and epigenomic factors render the cancerous cells aggressive, malignant and more lethal overall. One day, Curtis hopes, a blood-based analysis could detect that kind of aggressive cancer and its point of origination, all 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, their 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."

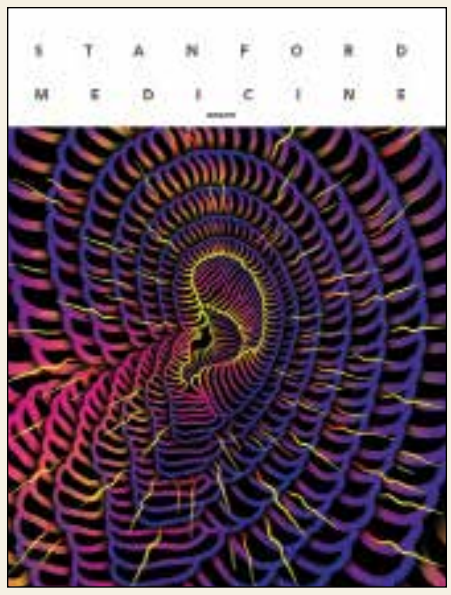
The future of PHIND

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 biomarker(s) 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 so far doled out $2.75 million to help catalyze basic, prevention-focused research at Stanford based on a competitive formal process. There were some 20 projects funded in the initial round. Earlier this month, the center officially announced the availability of an additional $1.5 million in seed funding. The goal is to launch up to 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." **ISM**

Spring issue of *Stanford Medicine* magazine explores the art, science of listening and hearing



By Patricia Hannon

Are you listening?

It's such a simple question, but your answer could be complicated, depending on who you are and why you're listening.

Someone with trouble hearing might be straining to hear family conversations. A scientist could be tracking distinct hums of various species of mosquito to help eliminate those that spread disease. A doctor might be listening to a patient's story for clues that can guide treatment.

The new issue of *Stanford Medicine* focuses on the importance of listening and hearing, and how new discoveries could improve both.

In his letter to readers, Lloyd Minor, MD, dean of the School of Medicine, explores why listening and hearing matter so much, and how new research could go a long way toward solving the mysteries of how we process sound and how it affects us physically and emotionally.

Minor and other physicians also discuss the unique relationship physicians have with people who are suffering. They say a care provider's ability to listen with compassion, empathy and understanding is as important as technical skills and that it's time to address the challenges of modern medicine that are harming their ability to connect with patients.

From singers to bioengineers

Throughout the issue, you'll find stories about the healing power of sound, as well as potential breakthroughs in treating hearing loss. Opera singer Renée Fleming explains why she is working with scientists to explore how music can improve overall health and well-being. Amy Yotopoulos, director of the Mind Division of the Stanford Center on Longevity, recalls her father's growing frustration and isolation as he started losing his hearing. Finding the right hearing aids helped him engage with his family again. The article describes why better and less costly devices are on the horizon.

Several stories explore breakthroughs in medicine and technology related to hearing, listening and sound:

• A professor of biophysics and of otolaryngology is working with a physician-scientist to redesign a popular class of antibiotics to prevent their side effect of hearing loss.

• Researchers are examining how birds regenerate crucial hearing cells so they can try to replicate the process in humans.

• In two examples of sound research, a bioengineer has developed an app to gather recordings of the hums of disease-carrying mosquitos to help eradicate them, and researchers are using sound waves to manipulate heart cells into patterns that resemble natural cardiac tissue to help heal heart disease.

• And given that machines are already listening to us, a Stanford group is among a coalition of people around the world who are unpacking the host of ethical, legal and social challenges of artificial intelligence in medicine. Yet the possibilities for how the information machines are capturing can be used for better diagnostics and treatment are intriguing: An AI researcher found that people speak more openly about problems to nonhuman listeners; two scientists are mining social media to learn more about the side effects of prescription drugs; and a composer and a neurologist are tapping into sound waves in the brain to detect seizures that are too minute to witness but that can still cause brain damage.

The issue also includes an essay from a doctor who uses a wheelchair and says it's time for the medical field to be more inclusive of people with disabilities, and a story and video about an infectious disease expert who builds kinetic sculptures to explain complicated science.

The magazine is available at stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at (650) 723-6911 or by sending an email to medmag@stanford.edu. **ISM**

Bereavement during pregnancy, child's mental health linked

By Beth Duff-Brown

Losing a loved one during pregnancy may affect the mental health of the child as he or she grows into adulthood, according to a study by two Stanford researchers.

"We find that prenatal exposure to the death of a maternal relative increases take-up of ADHD medications during childhood and anti-anxiety and depression medications in adulthood," wrote the researchers — Maya Rossin-Slater, PhD, assistant professor of health research and policy, and Petra Persson, PhD, assistant professor of economics — in the study, published in the April issue of the *American Economic Review*.

"Of course, you cannot prevent family members from dying, and we certainly do not want our findings to constitute yet another source of stress for expecting mothers, who already face rather intense pressure to eat the right foods, avoid activities deemed harmful, and experience an avalanche of health advice," Persson said. "But our findings potentially point to the importance of generally reducing stress during pregnancy, for example through prenatal paid maternity leave and programs that provide resources and social support to poor, pregnant women."


Maya Rossin-Slater

Their research focused specifically on singleton children in Sweden born between 1973 and 2011 whose mothers lost close relatives during their pregnancies. They used population registers to construct family trees that span four generations, from the children to their maternal great-grandparents. Their sample included all children whose mother lost a close relative — a sibling, parent, maternal grandparent, the child's father or her own older child — in the nine months after the child's date of conception or the year after the child's birth. The study did not account for the quality of those relationships.

Their analysis compared the outcomes of children whose mothers experienced a relative's death while they were pregnant with those of children whose maternal relatives died in the year after birth. They were thus able to isolate the impacts of fetal exposure to maternal stress from bereavement from all other consequences associated with a family member's death, such as changes to family resources or household composition, which affect all children in their sample.

Additionally, by considering the deaths of different relatives, the researchers' approach presents a new measure of intensity of stress exposure: the closeness between the mother and the relative who passed in the family tree.

Studying birth, medical records

Using birth and medical records, the researchers examined information about the children's health throughout childhood and into adulthood. They were aided by Sweden's novel prescription drug registry, which contains all prescription drug purchases and the exact substances and doses prescribed in the country.

"Our research suggests that policies that can reduce stress during pregnancy can have substantial benefits for the next generation," Rossin-Slater said. "Moreover, since poor families are more likely to experience stress than more advantaged ones, our results imply that stress-reducing policies that target low-income pregnant women could play a role in mitigating the persistence of socio-economic inequality across generations."

Persson and Rossin-Slater said they were initially inspired by two recent economic studies using data from Uganda and Iraq, which found that fetal exposure to malnutrition had adverse consequences for adult mental illness.

They wrote: "Our study offers complementary evidence linking early-life circumstance to adult mental health, but breaks new ground by focusing on stress, which may be more pertinent than malnutrition in modern developed countries such as the United States and Sweden, and by tracing health outcomes throughout the time period between the fetal shock and adulthood."


Petra Persson

Mental illness results in great financial and social costs. In 2008, the market for prescription drugs for depression totaled $9.6 billion in the United States alone, a sales volume exceeded only by cholesterol and pain medications.

In 2013, 1 in 7 school-age boys in the United States were treated with prescription drugs for attention deficit hyperactivity disorder, fueling a $9 billion market — five times larger than the $1.7 billion market just a decade earlier. The authors note that estimates also suggest mental illness accounts for more than half of the rise in disability costs among men in the last two decades.

"Our findings potentially point to the importance of generally reducing stress during pregnancy"

Moreover, in Sweden — the setting for their study — mental illness accounts for a larger share of health expenditures on prescription drugs than any other therapeutic class of medicines.

The scholars said that their study contributes to the research in this area by documenting a causal link between fetal stress exposure and mental health later in life. Moreover, by following the same children from birth to adulthood, they were able to observe the onset of adverse effects of exposure to maternal bereavement in utero.

'Far-reaching consequences'

"In sum, our results show that the death of a relative up to three generations apart during pregnancy has far-reaching consequences for mental health during childhood and adulthood," the researchers write.

Their findings that preventing fetal exposure to severe stress could result in large welfare gains: For example, based on the 2008 figure for the U.S. market, the 8 percent decrease in the consumption of prescription drugs for depression can be valued at around $800 million annually.

They conducted a back-of-the-envelope calculation to understand how exposure to economically induced stress during pregnancy might affect the mental well-being of the next generation by relying on past research estimating cortisol responses to grief and to economic shocks like unemployment and poverty.

"Our calculation suggests that in utero exposure to stress from unemployment may lead to a 17.3 percent increase in the likelihood of ever purchasing a drug to treat ADHD in middle childhood," they wrote, "and a 9 percent and 5.5 percent increases in the likelihoods of ever purchasing drugs to treat anxiety and depression in adulthood, respectively."

The newly published findings can inform one way by which policymakers and the medical community can tackle the prevalence and rising costs of mental health issues: by considering ways to make pregnancy — an inherently stressful time — a little easier to manage.

Rossin-Slater and Persson are both fellows at the at the Stanford Institute for Economic Policy and Research.

The research was supported by the Royal Swedish Academy of Sciences and by the Jan Wallander and Tom Hedelius Foundation. **ISM**

OBITUARY

Renowned microbe hunter Stanley Falkow dies at 84

By Krista Conger

Stanley Falkow, PhD, often proclaimed, "I never met a microbe I didn't like."

A professor emeritus of microbiology and immunology at the School of Medicine, Falkow spent most of his lifetime championing the cause of the tiny creatures that have coevolved to live peaceably with humans. He is considered by many to be the father of the field of bacterial pathogenicity — the study of how bacteria cause human disease.

He spoke out nationally against the routine use of antibiotics in animal feed and devoted himself to mentoring more than 100 students and postdoctoral scholars, many of whom went on to establish their own highly successful laboratories around the world.

His colleagues at Stanford and around the world are now mourning his loss.

Falkow died May 5 at his home in Portola Valley, California, due to complications of myelodysplastic syndrome and multiple subsequent strokes. He was 84. At his side were his wife and fellow Stanford professor Lucy Tompkins, MD, PhD; his friend, colleague and former student David Relman, PhD; and his longtime assistant Sara Fisher.

L.A. CICERO / STANFORD NEWS SERVICE

Stanley Falkow is considered the father of the field of bacterial pathogenicity. He died May 5.

"Without question, Stanley Falkow was a giant in the field of microbiology. But rather than his scientific accomplishments, he was most proud of the many students he happily mentored during his long career," said Lloyd Minor, MD, dean of the School of Medicine. "He invariably deflected any mention of his own successes and awards with a discussion of the many other individuals with whom he wished he could share the honor. He will be sorely missed, not just within the Stanford community, but around the world."

The joy of science

Colleagues and family members remember him for his devotion and selfless generosity to his students, his wry and self-deprecating wit and his uncanny ability to ask the creative, unexpected and insightful questions necessary to drive science forward to new discoveries. Outside the lab, he enjoyed fly-fishing in the Bitterroot River near his second home in Hamilton, Montana, tying flies and, later in life, piloting small aircraft.

During his career, Falkow identified the mechanisms by which antibiotic resistance spreads. He played a key role in the development of DNA cloning and served on a committee organized to assess the safety of recombinant DNA technology. Later in his career, he observed the dawn of large-scale DNA sequencing and immediately realized its potential to help him accomplish one of his fondest wishes: to identify the genetic changes that rendered usually harmless bacteria potentially deadly to their human hosts.

Falkow's research helped uncover the molecular causes of human diseases as varied as diarrheal disease, plague, food poisoning, whooping cough, ulcers and cat scratch fever. But, although his findings are directly applicable to human health, he arrived at his discoveries by approaching scientific problems from the viewpoint of the bacteria he found so endlessly fascinating.

"Stanley was one of these rare people who truly did live for and embody the joy of science," said Relman, professor of microbiology and immunology at Stanford and a former postdoctoral scholar in Falkow's laboratory. "For him, science was never a struggle. It was fun every moment along the way. And he showed that in his smile, in the lilt in his speech and even in the way he constructed his sentences. 'What a great question,' he'd say. Or 'I wonder why this might be?' He loved science for the beauty of it, for the intrigue, for the fun."

In 2008, Falkow, who was the Robert W. and Vivian K. Cahill Professor in Cancer Research, was honored with the Lasker-Koshland Award for Special Achievement in Medical Science — a prize often referred to as "America's Nobel." The special achievement award is given once every two years to commemorate a life of scientific contribution and service. More recently, Falkow was awarded the 2015 National Medal of Science for his studies of how bacteria can cause human disease and how antibiotic resistance spreads. But his proudest accomplishment was his election in 2007 to the United Kingdom's Royal Society as a foreign member.

"It meant the world to him," said Tompkins, the Lucy Becker Professor in Medicine and a professor of microbiology and immunology. "He was crying when he called me to tell me the news. He was such an anglophile, and this was such an incredible honor. When he was asked to sign the book of members — the same book signed by Charles Darwin and Christopher Wren — he was so nervous he dropped the quill pen on the floor. When he did sign, his signature was exceedingly tiny. He was so overwhelmed."

Falkow first made his mark in science by identifying the existence in bacteria of extrachromosomal circles of DNA known as episomes, or plasmids. He subsequently showed in a series of elegant experiments that these bits of DNA could be transferred even between distantly related bacteria to confer new traits on them, such as resistance to antibiotics or the ability to produce disease-causing toxins.

"I would call Stanley a scientist's scientist," said David Schneider, PhD, professor and chair of microbiology and immunology. "His experiments were beautiful. But more than that, his personality was exceedingly generous and his sense of humor helped to bring people together."

"Stanley lived and acted as if he was never going to run out of ideas," said Manuel Amieva, MD, PhD, associate professor of pediatrics and of microbiology and immunology and a former Falkow postdoctoral scholar. "He was incredibly generous, insisting that his students leave his lab not just with ideas for future research, but with whole projects and model animal systems with which to launch their own careers."

Finding inspiration in the library

Falkow was born in 1934 in Albany, New York. His father had immigrated from Kiev before World War I, and his mother was born in the United States after her family immigrated from Poland. His first language in the home was Yiddish. In 1943, his family moved to Newport, Rhode Island, and Falkow caught the bug bug.

"Somehow I discovered the public library and happened on a book called Microbe Hunters by Paul de Kruif," he recalled in a 2008 autobiographical career retrospective published in the Annual Review of Microbiology. "These microbe hunters became, and remain, my heroes. Their search to understand microbes was to me the most extraordinary adventure that I could imagine. It still is."

Dealing with anxiety

In 1955, Falkow started graduate school at the University of Michigan, but recurrent panic attacks soon caused him to drop out and return to his hospital job. Although he successfully completed graduate school and then postdoctoral studies — first at Brown University and subsequently at the Walter Reed Army Institute of Research — his ongoing anxiety and developing agoraphobia, about which he spoke freely, colored his early professional life.

A colleague at the hospital taught him how to fly fish in an attempt to alleviate his anxiety, sparking a lifelong love. In graduate school, Falkow discovered a new way that bacteria could transmit certain traits to one another through the transfer of plasmids, which are separate from bacterial chromosomes. One of these plasmid-transferrable traits was, crucially, the ability to break down compounds that would normally kill the bacterial cell.

Now at Georgetown, he and his students investigated the molecular basis of how plasmids encoding these antibiotic resistance factors, or R-factors, were transmitted between individual bacterium.

It was there that Falkow also discovered his love of teaching and mentoring, a skill he cultivated throughout his life. Many generations of students would benefit from Falkow's careful attention to this role.

Denise Monack, PhD, is one such example. For 14 years, she worked as Falkow's lab manager at Stanford, working and publishing alongside his students. But Falkow was concerned about her future, and he encouraged her to go to graduate school. As a result, Monack is now a professor of microbiology and immunology at Stanford, with an office next to Falkow's.

Public speaking never became easy, however. "Stanley was more comfortable in many ways around microbes than he was around people," Relman said. "We all saw him give talks many times. He would sweat bullets. It was really hard for him, and in some ways this anxiety brought out this kind of self-deprecating humor that made him immensely likable and effective."

"One of my greatest joys at Stanford has been teaching a course with Stan," said Justin Sonnenburg, PhD, associate professor of microbiology and immunology. "Although he was teaching with three junior faculty (and all of us idolized him), he always just acted like one of the crowd, and was always joking around. The only really bad part was having to lecture after him — his lectures were always a lively journey filled with wit and storytelling, and always saturated with brilliant insight that he made really accessible. There was no way to follow that act."

The mechanism of antibiotic resistance

At the Ciba symposium in 1968, Falkow was introduced to the idea that plasmids could transmit not just antibiotic resistance, but also the ability to make toxins that could harm the host cell and cause deadly diarrheal disease in animals and humans. He subsequently showed during his days as a faculty member at the University of Washington in Seattle that the genes that conferred these abilities could be swapped like trading cards between bacterial species to allow the rapid handoff of resistance or virulence in ways that vastly affect human health.

After the advent of DNA cloning, Falkow participated in the Asilomar conference of 1975, which was convened to provide guidelines for recombinant DNA experiments in bacteria and plasmids. He was also a member of a Food and Drug Administration committee investigating the routine use of antibiotics in animal feed — a practice which Falkow, knowing the ease with which antibiotic resistance can be transmitted between species, advocated against strongly.

"Stanley was often a mediator bringing together people with disparate opinions," said Stanley Cohen, MD, the Kwoh-Ting Li Professor in the School of Medicine at Stanford, who met Falkow in 1966 at Georgetown. "We worked closely together as members on many of these committees, and his scientific insight and creativity were always apparent. He had the unique ability to get to the heart of an issue with a humorous statement."

Arriving at Stanford

Partly at Cohen's urging, Falkow came to Stanford in 1981 to serve as the chair of microbiology and immunology. In 1983, he and Tompkins were married at Stanford's Memorial Church, and he began a new chapter of his life filled with travel and visits to the symphony and opera. In 2004, Falkow was diagnosed with myelodysplastic syndrome and given about two years to live. He devoted what he felt was his remaining time to turning over his research program to his former students Amieva and Monack. But every trainee held a special place in his heart.

"When he talked about one of his students, he would nearly cry," Tompkins said. "He was so proud of them all."

Falkow outlived his original prognosis by many years. And he never stopped asking questions and wondering what was around the next bend, whether in the river in which he loved to fish, in the experiments unfolding on the benches of his students or behind the next cloud on the horizon. At 72, he snuck out of his Montana home for flying lessons against Tompkins' wishes (she later relented and learned to fly herself as a precaution for when they flew together), and they loved soaring into the big Montana sky. At Stanford, he brought his golden retriever, Honey, to the lab every day.

Falkow's honors include the 2000 Robert Koch Prize, considered one of the most prestigious awards in the field of microbiology; election to the National Academy of Medicine; membership in the National Academy of Sciences and the Royal Society; and a former presidency of the American Society of Microbiology.

Falkow is survived by two daughters, Jill Brooks and Lynn Short; a stepson, Christopher Tompkins; his sister Jeanette Andriesse; and four grandchildren. ISM

Seaweed

continued from page 1

presumably healthful bacterial cultures naturally found in food such as yogurt or included in over-the-counter oral supplements — is an example of a growing public awareness of the importance of gut bacteria. Even if you don't take probiotics or eat yogurt, however, each of us unknowingly consumes low levels of gut-adapted microbes throughout our life. But, regardless of the source, it's not known what causes one strain to be successful over another. Many pass quickly through our digestive tract without gaining a foothold in our teeming intestinal carpet.

Sonnenburg and his colleagues wondered whether a dietary boost would give specific bacterial strains a leg up in the wild west of the gut microbiome. To investigate, they trekked to the San Jose Wastewater Treatment Facility to find members of the Bacteroides — the most prominent genus in the human gut microbiota — specifically looking for strains that are able to digest an ingredient relatively rare in American diets: the seaweed called nori used in sushi rolls and other Japanese foods. They screened the bacteria collected in the primary effluent for an ability to use a carbohydrate found in nori called porphyran.

"The genes that allow a bacterium to digest porphyran are exceedingly rare among humans that don't have seaweed as a common part of their diet," Sonnenburg said. "This allowed us to test whether we could circumvent the rules of complex ecosystems by creating a privileged niche that could favor a single microbe by allowing it to exist in the absence of competition from the 30 trillion other microbes in the gut."

Once they'd found a nori-gobbling strain of Bacteroides, the researchers attempted to introduce it into each of three groups of laboratory mice. Two groups of the mice had their own gut bacteria eliminated and replaced with the naturally occurring gut bacteria from two healthy human donors, each of whom donated exclusively to one group or the other. The third group of mice harbored a conventional mouse-specific community of gut microbiota.

A direct effect

The researchers found that when the mice were fed a typical diet of mouse chow, the porphyran-digesting strain was able to engraft in two groups of mice to varying and limited degrees; one of the groups of mice with human gut bacteria rejected the new strain completely. However, when the mice were fed a porphyran-rich diet, the results were dramatically different: The bacteria engrafted robustly at similar levels in all the mice. Furthermore, Shepherd found that she could precisely calibrate the population size of the engrafted bacteria by increasing or decreasing the amount of nori the animals ingested.

"The results of this dilution experiment blew us away," Sonnenburg said. "The direct effect of diet on the bacterial population was very clear."

In addition to showing that they could favor the engraftment and growth of the nori-gobbling bacterial strain, the researchers went one step further by showing that the genes necessary to enable the digestion of porphyran exist as a unit that can be engineered into other Bacteroides strains, giving them the same engraftment advantage. Now they're working to identify other genes that confer similar dietary abilities.

"We can use these gene modules to develop a vast toolkit to make therapeutic microbial treatments a reality," Sonnenburg said. "Porphyran-digesting genes and a diet rich in seaweed is the first pair, but there could potentially be hundreds more. We'd like to expand this simple paradigm into an array of dietary components and microbes."

The researchers also envision developing bacteria that harbor kill switches and logic gates that will permit clinicians to toggle bacterial activity on and off at will, or when a specific set of circumstances occur.

"It's become very clear over the last 10 years that gut microbes are not only wired to many aspects of our biology, but that they are also very malleable," Sonnenburg said. "Our growing ability to manipulate them is going to change how precision health is practiced. A physician whose patient is about to begin immunotherapy for cancer may choose to also administer a bacterial strain known to activate the immune system, for example. Conversely, a patient with an autoimmune disease may benefit from a different set of microbiota that can dial down an overactive immune response. They are just a very powerful lever to modulate our biology in health and disease."

Stanford graduate student Kali Pruss is a co-author of the study. Researchers from Novome Biotechnologies also co-authored the study.

The research was supported by the National Institutes of Health and the National Science Foundation.

Stanford's Department of Microbiology and Immunology also supported the work. ISM

Multigene

continued from page 1

26 percent of those tested in early 2013 to about 66 percent in mid-2015. Conversely, the proportion of women who received BRCA-only testing during the same time period decreased from about 74 percent to about 34 percent.

Multigene panel testing was about twice as likely as BRCA-only testing to identify disease-associated mutations. But it was also more likely to reveal mutations of uncertain clinical significance, particularly in racial or ethnic minorities. This disparity is likely due to the fact that most genes were sequenced first in white patients, and the causative effect of variations in other minorities is not clear. This finding emphasizes the need for research in diverse populations to clarify genetic uncertainty and reduce racial disparities in the clarity of genetic test results, the researchers say.

"More genetic counselors are needed."

Timing of tests varied

The timing of the tests also varied, the study found. Although the majority of the women tested got their results prior to surgery to remove the tumor, many did not. About 33 percent of women receiving multigene panel testing were tested after surgery, versus about 20 percent of women receiving BRCA-only testing — perhaps due to a recognition by clinicians that interpreting the results of a multigene panel can be complex and requires the expertise of genetic counselors, who are not always rapidly available.

"Furthermore, patients and their clinicians may view genetic testing as a lower priority than tumor biology and pathology testing which most directly inform the treatment options." said Katz.

"As genetic testing has become more comprehensive and less expensive, we have begun to see a significant problem in terms of the genetic-counselor workforce," Kurian said. "More genetic counselors are needed, and they should be integrated into routine cancer care. There is also a need for new care-delivery models that effectively triage appropriate patients to timely genetic counseling."

Researchers from the University of Southern California, Emory University and the Memorial Sloan-Kettering Cancer Center also contributed to the study.

The research was supported by the National Institutes of Health, the National Cancer Institute and the University of Michigan Cancer Center.

Stanford's departments of Medicine and of Health Research and Policy also supported the work. ISM

Tracer

continued from page 1

study. Gambhir, the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research, is the senior author.

Two for one

The tracer was born out of a collaboration with Ronald Levy, MD, professor of oncology, who was in the process of devising what's now considered a promising cancer "vaccine." The goal of the vaccine — which is different from a traditional preventive shot because it works more as an injected immunotherapy — is to prompt the T cells into an activated state and get them to attack tumors in the body. But cancer therapies are not often one-dose-fits-all. So the question became: Is there a way to know, right away, if the vaccine is working?

"Our challenge was to find a molecule that's almost exclusively present on activated T cells — not just any T cell — because there are many T cells that just sit around resting," Gambhir said. By coincidence, the molecule he found was the same one that Levy harnessed in his vaccine, a protein on the surface of activated T cells called OX40.

Boiled down, Levy's cancer vaccine is a package of two stimulating agents. One coaxes T cells into producing OX40 on their surface; the other binds to OX40 and enables the cell to engage with tumor cells. Together the tag-team agents essentially prod loafing immune cells into high gear.

The tracer scours the entire body in search of cancer-killing T cells.

Once the tracer is injected, it scours the entire body, including the immune system, in search of cancer-killing T cells — but only those laden with OX40. Upon meeting, the tracer binds to OX40 and, when hitched together, the radioactive complex glows under a PET scan, revealing only those T cells that have been successfully activated, ready to ravage the tumor. If the scan comes back with low to no signal in the tumor or tumors, it's an indication that doctors (in theory, as the vaccine and tracer have only been tested in mice) ought to reevaluate the immunotherapy dosage or change the treatment course altogether.

The power of PET

Gambhir's lab tested the tracer first in cell cultures. They found that the compound was able to suss out activated T cells about 95 percent of the time. Later in mouse models, they still saw success overall, but it was a bit more subdued. In a group of about 50 mice, the PET tracer performed accurately upward of 90 percent of the time.

"It's really only now that this tactic is coming into play; the PET scan is usually focused on assessing only the tumor cells," said Gambhir. "But now, with new imaging agents like this, we're able to image the immune cells, and that's really the second half of the equation."

Gambhir acknowledges that one could simply wait to see physical changes in the tumor volume to determine whether the therapy is working. But that poses a problem. It may take weeks, or even months, to definitively see whether the cancer is responding to the treatment. Say the vaccine doesn't work. In the time it took to find out, the cancer would have continued to spread, becoming more molecularly heterogeneous and even more difficult to treat the next time around. Knowing sooner gives the patient more time to try other options, hopefully leading to better outcomes.

Clinical trial

Levy has moved his vaccine into a phase-1 clinical trial. In the next few months, Gambhir plans to move this new OX40 tracer into that same clinical trial, so that the tracer and therapy can be tested in conjunction.

"We were able to predict what was going to happen in mice several weeks out by looking only 48 hours from the start of the immunotherapy. We could figure out which mouse was going to respond to the immunotherapy and which wasn't before they actually did or did not respond," Gambhir said. "And that's exactly what we're trying to do. We're trying to show that this approach can, in humans, allow us to image early and thereby let us evolve the therapy quickly."

Gambhir also is pursuing work to establish the OX40 tracer as a diagnostic for other applications, such as the autoimmune disease multiple sclerosis. "It's important to remember that this is a really general approach to visualizing activated T cells — this shouldn't be thought of as specifically for cancer immunotherapy alone," he said. "That's just one important application."

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

Other Stanford co-authors of the study are Idit Sagiv-Barfi, PhD, instructor of oncology; Kezheng Wang, MD, PhD, a visiting faculty member in the Gambhir lab; postdoctoral scholar Ophir Vermesh, PhD; Debra Czerwinski, life science research assistant; Emily Johnson, life science research professional; and Michelle James, PhD, assistant professor of radiology and of neurology and neurological sciences.

Gambhir and Levy are members of Stanford Bio-X and the Stanford Cancer Institute. Gambhir is also a member of the Stanford Cardiovascular Institute and the Stanford Neurosciences Institute.

A researcher at Harbin Medical University also contributed to this work.

The study was funded by the Ben & Catherine Ivy Foundation, the Canary Foundation, the National Cancer Institute and the Leukemia and Lymphoma Society.

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

Sheila Dolezal, 'team player extraordinaire,' wins Amy J. Blue Award

By Kathleen J. Sullivan

When Sheila Dolezal arrives at her office on the third floor of Stanford Hospital, there is one thing she knows for certain — that there will be nothing "typical" about her workday.

"One day I can come in and spend the entire day in one-on-one meetings with staff members, and the next day, I can be working on a business plan to expand clinical care in underserved areas or to introduce a new service in a clinic," said Dolezal, the director of finance and administration in the Department of Obstetrics & Gynecology at the School of Medicine.

L.A. CICERO / STANFORD NEWS SERVICE

Sheila Dolezal (center), who won an Amy J. Blue Award, meets with members of her team.

"I could be working on issues related to human resources, operations, financial or strategic planning. My job includes many responsibilities, and that makes it really exciting."

While there is no such thing as a typical workday, Dolezal said every day has one thing in common.

"I am surrounded by people who are very passionate about women's issues and women's health and women's empowerment," said Dolezal, who joined the department in 2000 and handles financial and administrative affairs for about 120 people, including 50 professors, 50 researchers and 20 staff members. "It makes me feel so good to be part of that. I love the idea that I am contributing in some way to advancing the position of women."

The colleagues who nominated Dolezal for a 2018 Amy J. Blue Award said she helps hold the large and complex department — and its seven divisions — together.

"In addition to her superb leadership, organizational and technical skills, Sheila is a team player extraordinaire," one group of professors wrote. "She embraces everyone and anyone even remotely affiliated with our department as an essential part of our overall success, and they certainly don't need an MD title following their name to be part of the family. She has a remarkable way of letting you know that you are a valued part of our overall mission."

Dolezal is one of three Stanford employees who were recently named 2018 Amy J. Blue Award winners. The award honors staff members who are exceptionally dedicated, supportive of colleagues and passionate about their work.

The other winners are Christina Ablaza, the program manager of the Creative Writing Program, and Rafael Velazquez, a food service worker in Stanford Dining, a division of Residential & Dining Enterprises.

Stanford President Marc Tessier-Lavigne presented the awards at a May 15 ceremony for the winners and their families, friends and colleagues. . The award, which was established in 1991 to honor the life and work of Amy J. Blue, an associate vice president for administrative services and facilities, includes a $4,000 prize.

A career change led to Stanford

Dolezal, who was born and grew up in Santa Clara, California, earned a bachelor's degree in organizational behavior at the University of San Francisco.

After graduating, she served as a branch manager of a savings-and-loan in nearby Sunnyvale, California, but realized after a few years that the job wasn't a good fit.

She decided to follow her late mother's advice: "If your heart's not in it, find where your heart is."

Dolezal found her heart and her passion at Stanford.

"I witnessed firsthand the many health and other struggles my mother experienced in life, and I have always wanted to be part of a mission and vision to advance a woman's place in society, and health care is a foundational element of this vision," she said. "I was so impressed by how Stanford had cared for my younger sister, who had several orthopedic surgeries here, and the care they gave to my mother, who had diabetes. So I had a deep respect for this institution as a whole. When I had the opportunity to join Stanford in 1990, I grabbed it."

Dolezal worked in the hospital's admitting office for about four years, then joined the finance and administration staff in the Department of Radiology. Some five years later, she joined the Department of Obstetrics & Gynecology.

Commended for dedication, grace, humor

Colleagues who nominated Dolezal for the Amy J. Blue Award said her door is always open:

"As busy as she is, Sheila somehow finds the time to genuinely listen to and care for the myriad of people who seek her out. From faculty member to administrative staff, from fellow-in-training to resident, she is there to listen to concerns, provide meaningful feedback and help chart a path forward. She is a mentor to so many, including young administrative and research managers trying to develop a skill set in how to create productive, nurturing teams. She is a caring, special, can-do person. It is hard for us to imagine this department without her."

Colleagues also praised Dolezal's "inclusive and pervasive" sense of humor:

"I have heard laughs ring out during the most serious of finance meetings, easing tensions and bringing everyone into the fold. She wins over others quickly with joy and warmth, and sees well-timed opportunities for levity in the midst of the sometimes 'heavy' hospital setting. Her authenticity in this joy is so engaging and endearing, that, when taken together with her strategic mind, it is clear why she has had such an impact on the people in this department."

Professors said Dolezal was instrumental in the establishment of gynecologic oncology services at the new Stanford Cancer Center South Bay in San Jose, California, and at Stanford Health Care's ValleyCare Medical Center in Pleasanton, California, and played a key role in launching and expanding the department's faculty midwifery program.

"In addition to her in-depth knowledge of finances and business aspects that are important to the viability of our entire department, Sheila has a profound understanding of the systems and workflows within the School of Medicine and the two hospitals — Stanford Health Care and Lucile Packard Children's Hospital," one professor wrote.

> "She wins over others quickly with joy and warmth."

"It is difficult to imagine a more accomplished and knowledgeable director of finance and administration for any department. On top of this, Sheila has extraordinary people skills and an always positively reinforcing attitude that percolates not only through the administrative staff, but the entire department, including faculty, fellows, resident and students. By all measures, Sheila is a more-than-worthy recipient of the Amy J. Blue Award." ISM

OF NOTE

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

Katherine Blevins

Vivian de Ruijter

Eric Kramer

Michael Eisenberg

Melanie Hayden Gephart

John Ioannidis

Sun Kim

Michael Khodadoust

Gordon Lee

Resident **KATHERINE BLEVINS**, MD, and postdoctoral scholars **VIVIAN DE RUIJTER**, MD, and **ERIC KRAMER**, PhD, received a 2018 Translational Research Award from the Wallace H. Coulter Foundation. The $100,000 award includes mentoring and oversight to help advance their large-bore arterial closure technology toward patient care.

MICHAEL EISENBERG, MD, was promoted to associate professor of urology, effective March 1. He specializes in male infertility and sexual health, with a research focus on surgical innovation, epidemiologic studies and basic science discoveries to improve the treatments, outcomes and reproductive health of men.

MELANIE HAYDEN GEPHART, MD, was promoted to associate professor of neurosurgery, effective March 1. Her research focuses on understanding the genetic and epigenetic mechanisms driving tumor formation and disease progression in malignant brain tumors.

JOHN IOANNIDIS, MD, DSc, professor of medicine and of health research and policy and the C.F. Rehnborg Professor in Disease Prevention, received the 2018 Alexandra Jane Noble Science Courage Award from Novim. The award "recognizes those who speak out professionally as well as scientifically to correct a misimpression or right a wrong in the name of science and public understanding," according to the nonprofit institute, based in Santa Barbara, California.

SUN KIM, MD, was promoted to associate professor of medicine, effective March 1. She specializes in treating Type 2 diabetes, polycystic ovarian syndrome and obesity, with a research focus on the pathophysiology and treatment of Type 2 diabetes.

MICHAEL KHODADOUST, MD, PhD, was appointed assistant professor of medicine and of dermatology, effective March 1. His research focuses on examining how the body's immune system fights cancer cells and developing immune-based therapies for the treatment of T-cell lymphomas.

GORDON LEE, MD, was promoted to professor of surgery, effective April 1. He is the residency program director for plastic surgery and director of microsurgery. He specializes in surgical education and training in plastic surgery, and his research interests include understanding and improving outcomes and developing new techniques in microsurgery and reconstructive surgery.

CLEMENT MARSHALL, MD, resident in surgery, was a co-recipient of the 2018 Thomas R. Russell, MD, FACS, Research Paper Competition Award from the Northern California Chapter American College of Surgeons. He was honored for the paper, "Gene expression analysis in abdominal adhesion formation." ISM