INSIDE STANFORD MEDICINE

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A low-cost fix substantially improves images from a widely used optical scanning technique.
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Grads urged to promote health care equality

By Tracie White

STEVE FISCH

Medical school graduates proceed to the diploma ceremony, which was held June 17 on the lawn next to the Li Ka Shing Center for Learning and Knowledge.

Fifty-six years after giving a speech as the first African-American graduate of the Stanford School of Medicine, Augustus White, MD, PhD, returned to the podium of his alma mater with gray hair and a strong message.

"I believe that health care should be an inalienable human right," White said, addressing the School of Medicine's graduating class of 2017 at the June 17 diploma ceremony. "We must work hard so that we come as close as possible to that ideal."

Lloyd Minor MD, dean of the School of Medicine, introduced White, an orthopaedic surgeon who served for 13 years as chief of surgery at Harvard School of Medicine, as a "pioneering visionary" committed to the rights of underrepresented minorities in medicine.

"We as a nation can and must do better than our present state of politicized and dysfunctional health care," White said.

He advocated for mending a health care system that he said still doesn't provide equal health care for all. "'Of all the forms of inequality, injustice in health care is the most shocking and inhumane,'" White said, quoting Martin Luther King Jr.

Caps, gowns and heat

The diploma ceremony was held on a hot afternoon under a giant tent on the lawn next to the Li Ka Shing Center for Learning and Knowledge. It was dedicated to the memory of Maria Birukova, a graduate student in the MD-PhD program who died in a rock-climbing accident in 2016.

The audience was filled with proud mothers and fathers, fidgety children in fancy clothes, aunts and uncles and cousins and friends. With balloons and flowers, they cheered in support of the new class of graduates, which included 65 students earning a medical degree, 53 earning a PhD and 52 earning a master's degree.

"Congratulations!" Minor said. "You made it!"

Prior to the ceremony, graduating students, dressed in caps and gowns, congregated inside the Li Ka Shing Center, preparing to walk on stage. They took photos and hugged one another, bidding goodbye as they prepared to begin the next stages of their lives.

"It feels a bit surreal," said Michelle Nguyen, MD, who already started the first few days of her residency in internal medicine at University of Pittsburgh and flew back for See GRADUATION, page 6

Newly identified process of gene regulation challenges accepted science, researchers say

By Krista Conger

Researchers at the School of Medicine have discovered an unexpected layer in the regulation of gene expression. The finding will likely disrupt scientists' understanding of how cells regulate their genes to develop, communicate and carry out specific tasks throughout the body.

The researchers found that cellular workhorses called ribosomes, which are responsible for transforming genes encoded in RNA into proteins, display a never-before-imagined variety in their composition that significantly affects their function. In particular, the protein components of a ribosome serve to tune the tiny machine so that it specializes in the translation of genes in related cellular pathways. One type of ribosome, for example, prefers to translate genes involved in cellular differentiation, while another specializes in genes that carry out essential metabolic duties.

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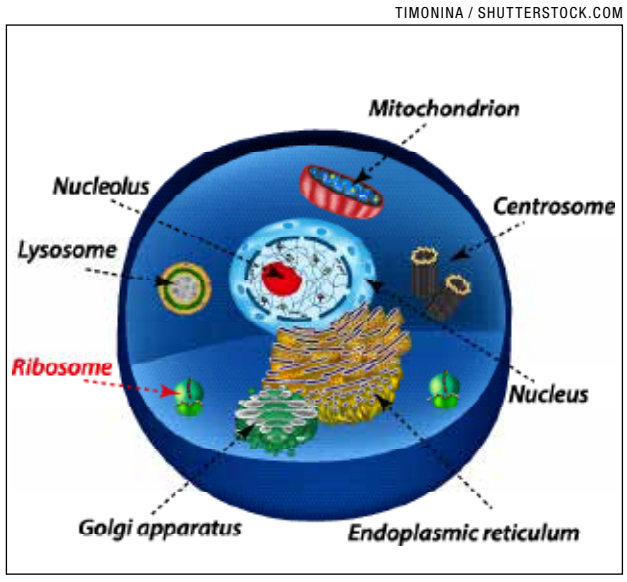

Ribosomes in a cell transform genes encoded in RNA into proteins.

The discovery is shocking because researchers have believed for decades that ribosomes functioned like tiny automatons, showing no preference as they translated any and all nearby RNA molecules into proteins. Now it appears that broad variation in protein production could be sparked not by changes in the expression levels of thousands of individual genes, but instead by small tweaks to ribosomal proteins.

'Broad implications'

"This discovery was completely unexpected," said Maria Barna, PhD, assistant professor of developmental biology and of genetics. "These findings will likely change the dogma for how the genetic code is translated. Until now, each of the 1 to10 million ribosomes within a cell has been thought to be identical and interchangeable. Now we're uncovering a new layer of control to gene expression that will have broad implications for basic science and human disease."

Barna is the senior author See RIBOSOMES, page 7

Inflammatory molecule essential to muscle regeneration, study finds

By Krista Conger

A molecule released as part of an inflammatory response after muscle injury or rigorous exercise activates muscle stem cells responsible for repairing the damage, according to a study by researchers at the School of Medicine.

Treating laboratory mice with a dose of the molecule, a lipid metabolite called prostaglandin E2, just after injury accelerates the See MUSCLE, page 7

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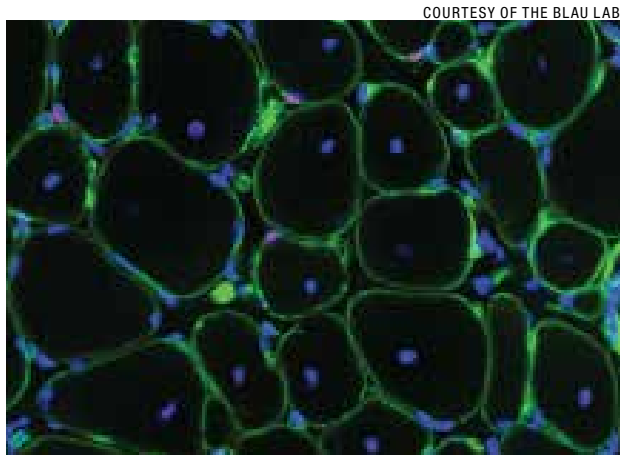


This cross-section of regenerated muscle shows muscle stem cells (red) in their niche along the muscle fibers (green). The blue dots are DNA in the nuclei of the fibers.

Thousands of genes influence most diseases, researchers say

By Jennie Dusheck

A core assumption in the study of disease-causing genes has been that they are clustered in molecular pathways directly connected to the disease. But work by a group of researchers at the School of Medicine suggests otherwise.

The gene activity of cells is so broadly networked that virtually any gene can influence disease, the researchers found. As a result, most of the heritability of diseases is due not to a handful of core genes, but to tiny contributions from vast numbers of peripheral genes that function outside disease pathways.

Any given trait, it seems, is not controlled by a small set of genes. Instead, nearly every gene in the genome influences everything about us. The effects may be tiny, but they add up.

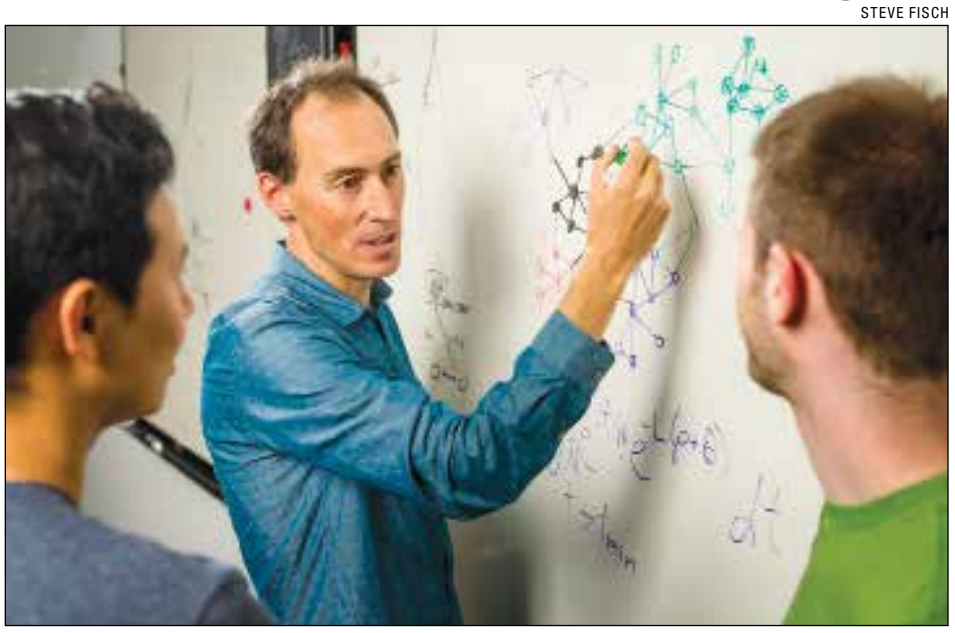
The work is described in a paper published June 15 in *Cell*. Jonathan Pritchard, PhD, professor of genetics and of biology, is the senior author. Graduate student Evan Boyle and postdoctoral scholar Yang Li, PhD, share lead authorship.

The researchers call their provocative new understanding of disease genes an "omnigenic model" to indicate that almost any gene can influence diseases and other complex traits. In any cell, there might be 50 to 100 core genes with direct effects on a given trait, as well as easily another 10,000 peripheral genes that are expressed in the same cell with indirect effects on that trait, said Pritchard, who is also a Howard Hughes Medical Institute investigator.

Each of the peripheral genes has a small effect on the trait. But because those thousands of genes outnumber the core genes by orders of magnitude, most of the genetic variation related to diseases and other traits comes from the thousands of peripheral genes. So, ironically, the genes whose impact on disease is most indirect and small end up being responsible for most of the inheritance patterns of the disease.

"This is a compelling paper that presents a plausible and fascinating model to explain a number of confusing observations from genomewide studies of disease," said Joe Pickrell, PhD, an investigator at the New York Genome Center, who was not involved in the work.

STEVE FISCH



Jonathan Pritchard (center) and his colleagues, Yang Li (left) and Evan Boyle found that the gene activity of cells is so broadly networked that virtually any gene can influence disease.

From a polygenic to omnigenic model

Until recently, said Pritchard, he thought of genetically complex traits as conforming to the polygenic model, in which genes have direct effects on a trait, whether that trait is something like height or a disease, such as autism.

But last year, while putting together a paper on the recent evolution of height in northern Europeans, Pritchard was forced to rethink that idea.

In the earlier work on the genetics of height, Pritchard and his colleagues were surprised to find that essentially the entire genome influenced height. "It was really unintuitive to me," he said. "To be honest, I thought that it was probably wrong." His team spent a long time trying to understand the surprising result.

Implications for science

"I gradually started to realize that the data don't really fit the polygenic model," Pritchard said. That work led directly to the current *Cell* paper, he said. "We started to think, 'If the whole genome is involved in a complex trait like height, then how does that work?'"

Pritchard's omnigenic model promises to take biology in new directions and means scientists need to think a lot more about the structure of networks that link together those thousands of peripheral disease genes.

"If this model is right," said Pritchard, "it's telling us something profound about how cells work that we don't really understand very well. And so maybe that puts us a little bit further away from using genomewide association studies for therapeutics. But in terms of understanding how genetics encodes disease risk, it's really important to understand."

This research was supported by the National Institutes of Health, the National Science Foundation and the Howard Hughes Medical Institute.

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

Office of Communication & Public Affairs wins six national awards from CASE

By Susan Ipaktchian

The School of Medicine's Office of Communication & Public Affairs has received national recognition for the quality of its news releases and magazine stories, including the top prize in the "best articles of the year" category.

Overall, the office received six awards — one platinum award, two golds and three silvers — in the 2016 Circle of Excellence Awards contest sponsored by the Council for the Advancement and Support of Education.

Writer Tracie White earned the sole platinum award in the best-articles category for "The puzzle solver," which was published in the spring 2016 issue of *Stanford Medicine* magazine. The article described the efforts of genetics professor Ron Davis, PhD, to find a cure for chronic fatigue syndrome, the crippling illness afflicting his son. Contest judges said it was "a powerful story, deeply compassionate and compelling in its expression. The reader feels this family tragedy while also appreciating the science being done at Stanford." This is the second time that White has won the platinum award in the category.

JASON HOLLEY

This illustration received a silver award in the annual CASE Circle of Excellence Awards.

The office also won a gold award for periodical staff writing. Judges said the magazine stories "met the difficult task of relaying complex medical and scientific ideas clearly and concisely, in a way that appeals to both lay readers and a professional audience, and did so while drawing readers in with compelling writing that emphasizes the human aspect behind the science. The articles demonstrated 'how' Stanford is on the forefront of medical education, research, and development, yet each story was written with a focus on the human perspective-which demonstrates the 'why.'"

The five stories in the staff-writing entry included:

- White's "puzzle solver" story.
- "And yet you try," by Julie Greicius, published in the fall 2016 issue, which describes the quest of diagnostics expert Sam Gambhir to save his son after the teen was diagnosed with a brain tumor. Greicius' story also received a silver award in the feature-writing category.
- "Inflammation implication," by Bruce Goldman, exploring research into how age-related chronic systemic inflammation may affect your heart.
- "Diagnose this," by Jennie Dusheck, which tells how researchers in the field of diagnostics are taking advantage of advances in biomedical research, engineering and computer technology to make diagnostics more informative and less invasive. The story led off the fall 2016 issue focusing on the field of diagnostics.
- "Brain waves," by White. This feature, from the winter 2016 issue on precision health, shows how insights from neuroscience could customize care for people with anxiety, depression and other psychiatric conditions.

The news releases written by the office's staff earned a gold award in the research, medicine and science news writing category. The judges commended the entry for "high-end writing" that "presents topics in ways in which the average reader can peruse them comfortably. Good use of quotes, which drive but do not overpower the writing." The news releases were edited by John Sanford.

The five news releases included in the entry were:

- "Tweak in gene expression may have helped humans walk upright," by Krista Conger.
- "Blood test could transform tuberculosis diagnosis," by Dusheck.
- "Stem cells shown safe, beneficial for chronic stroke patients," by Goldman.
- "Researchers predict with high accuracy if antidepressants will help," by White.
- "Common prostate cancer treatment liked to later dementia," by Dusheck.

Stanford Medicine magazine received a silver award in the special-constituency magazine category. Judges cited the magazine for "deeply personal and affecting" stories and for exploring "pressing issues affecting health care, often detailing the human impact on physicians, patients and families." The magazine is edited by Rosanne Spector and Kathy Zonana.

An illustration by Jason Holley that accompanied the story "Building a better drug" in the winter 2016 issue of the magazine won a silver award in the design category. Judges said the drawing "showed strength in the forced perspective, the asymmetry and the abstract narrative of the background."

CASE is a professional organization for those in the fields of communications, alumni relations and development at educational institutions. It includes more than 3,600 colleges, universities, and independent elementary and secondary schools in 82 countries. To recognize the best work in these fields, CASE sponsors its annual Circle of Excellence Awards. ISM

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Stanford Medicine publishes inaugural health care trends report

Stanford Medicine on June 19 published its inaugural Health Trends Report, a comprehensive review and analysis of existing health care research and open-source data, combined with insights from Stanford faculty and external health care experts, on the current and emerging trends facing the health care sector.

The report, which will be published annually, found the promise and challenge of big data to be the most important forces driving change and improvements across health care.

Findings

The report outlines how all stages of the medical experience are being affected by big data, beginning with medical research and extending into and beyond the doctor's office.

However, its most crucial finding is the need to train doctors and other medical professionals for a future in which analyzing and managing big data will be a core part of their roles. Improving their skills and literacy in computing and analytics, data management and assessment, information processing and software and technology-infrastructure development will be vital if the profession is to take advantage of the benefits of big data. This will require changes to how health care providers are taught the skills to deliver successful patient outcomes.

Similarly, the rise in wearable devices, genetic testing and other technologies gives patients more information than ever about their own health, making greater efforts to promote health literacy necessary so they can make informed decisions.

'An opportunity and a challenge'

"Today, health care is becoming increasingly connected but also increasingly complex. This unique dichotomy poses both an opportunity and a challenge for institutions like our own, whose job it is to heal, innovate and educate," said Lloyd Minor, MD, dean of the School of Medicine. "In publishing this report, we hope to show how big data is the most important trend facing the sector and, in the process, inform and educate the entire medical community —including patients, doctors, the private and public sectors — who are actively shaping the future of health care."

"As big data becomes more of a resource for patients and their physicians, it simply is not enough to stick to the traditional ways of conducting research, engaging in patient care and educating the next generation of doctors," he added. "Institutions like Stanford have a responsibility to drive advances in data management so that patients can be partners in their own care. By leveraging big data, we can create a vision of health care that is more preventive, predictive, personalized and precise."

The report suggests that the following areas must be prioritized if the impact of big data in health is to be fully realized:

• Doctors and other members of the medical community must be more data literate and skilled in data analytics.

• Health care organizations need to have the right systems, processes and structures in place to manage big data.

• Silos and roadblocks across health care organizations that prevent effective data-sharing must be broken down, but protecting the privacy and security of patient data is paramount.

• Encouraging patients to take an active role in their own care and adopt healthier lifestyles remains critical, if challenging.

• Rising costs across the U.S. health care system threaten to undermine the role big data can play.

• Reforms to electronic health records through the use of better technology and data management will help doctors provide more personalized patient care.

An online version of the report, including the executive summary, can be found at med.stanford.edu/healthtrends. Print copies of the report can be requested at 850-1265. ISM

Immune cells tied to heart patients' increased risk of shingles

By Bruce Goldman

People with coronary artery disease are vulnerable to getting shingles, a painful skin rash. But why this is so has been a mystery.

Now, School of Medicine researchers have traced the connection to a defective immune cell's sweet tooth.

In a study published online June 12 in the *Journal of Clinical Investigation*, the researchers learned that a set of immune cells whose aberrantly large appetite for glucose predisposes people to this heart condition also disables the immune response to viral infections — and does so using the same immune-response-derailing technique often employed by cancer cells.

Our increasing vulnerability to shingles as we age speaks to our immune system not being as capable as when we're younger, said Cornelia Weyand, MD, professor and chief of immunology and rheumatology. "But how this would be related to heart disease has been an open question, until now," she said.

Shingles' incidence increases exponentially after age 50. About half of all people who are 80 years old have had experienced a shingles attack. It's a leftover from childhood infection by varicella zoster, the virus that causes chickenpox. Even after our immune system defeats the active infection when we're young, the virus lives on inside our nerve ganglions. In older or immune-compromised people, the long-dormant virus can reactivate, crawl along the nerve fiber and emerge at nerve endings as a painful skin rash that's exceedingly difficult to treat.

In about 20 percent of shingles cases, the excruciating pain persists long after the rash clears up, said Weyand, the study's senior author. The lead authors are postdoctoral scholar Ryu Watanabe, MD, PhD, and former postdoctoral scholar Tsuyoshi Shirai, MD, PhD, now at Tokohu University in Japan.

"Coronary artery disease patients' glucose-guzzling macrophages, it turns out, exert the same paralyzing effect on T cells that cancers cells do, in much the same way," Weyand said.

A heart attack is born

An earlier study by Weyand's group showed that macrophages — immune cells essential to battling infections and repairing injured tissue — in patients with coronary artery disease boast excessive amounts of molecules involved in the uptake of glucose, forcing accelerated metabolism of the sugar.

Macrophages are attracted to wound sites, including coronary artery vessels bearing tiny scars or tears wrought by, say, high blood pressure. Weyand's earlier study demonstrated that while macrophages dwelling in arterial plaque may have good intentions, if they're predisposed to glucose gluttony they can go off-task, become inappropriately inflammatory and exacerbate the problem. The inflammatory macrophages both accelerate plaque buildup in coronary arteries and render that plaque brittle. It's when a chunk of labile plaque breaks off, suddenly blocking blood flow, that a heart attack is born. Coronary artery disease accounts for half of all deaths in the United States.

Macrophages also initiate helpful immune responses. The term "macrophage" derives from the Greek words for "big eater." These cells routinely gnaw on any pathogen they encounter, displaying bits of the ingested microbe on their surface for inspection by other immune cells called T cells, which can spearhead a targeted assault on the pathogen.

But, the new study showed, glucose-addicted macrophages that abound in atherosclerotic lesions are beyond incompetent at spurring T cells' antiviral activity. The aberrant macrophages actively discourage it.

So do tumor cells. Cancer-cell surfaces frequently manifest abundant amounts of a surface molecule, PD-L1, whose corresponding receptor, PD1, appears on T cells. The binding of PD1 to PD-L1 sets off a biochemical cascade inside a T cell, short-circuiting the fury it would otherwise mount on contact. Recent medical progress in understanding and exploiting this "immune checkpoint" mechanism has revolutionized cancer therapy.

"Blocking PD1/PD-L1 interaction is the object of a whole new wave of cancer-therapeutic interventions," said Weyand. "Many hundreds of clinical trials of this approach, which unleashes cancer patients' immune response to their cancer cells and unlike chemotherapy is not toxic to other cells, are underway."

Experiments by Weyand and her colleagues drew on the knowledge that macrophages, too, express PD-L1 on their surfaces.

Immune response restored

The investigators obtained blood and tissue samples from 113 patients with coronary artery disease who had sustained at least one heart attack and from 109 demographically matched healthy control subjects. From participants' blood samples, the scientists extracted cells called monocytes that begin life in the bone marrow, circulate in blood and, on taking up residence in a tissue, mature into full-blown macrophages. The scientists induced this maturation in culture.

NORBERT VON DER GROEBEN

Cornelia Weyand and her team determined that people with coronary artery disease face an elevated risk for shingles because aberrant immune cells dial down the body's immune response to viral pathogens.

"Your T cells' ability to stave off shingles is a good proxy for your overall ability to fight off new pathogens, the re-emergence of old ones or cancer," said Weyand. T cells targeting varicella zoster get aroused on contact with macrophages displaying pieces of this virus on their surfaces. So, the researchers fed viral bits to monocyte-derived macrophages from either the patients or the control subjects, and then gauged reactions of T cells incubated in a dish with these cells. One-third as many T cells exposed to virus-displaying macrophages from the patients mounted a reaction compared with T cells exposed to macrophages from the age-matched control subjects.

Antibodies that interfere with the PD1/PD-L1 checkpoint happen to be easy for researchers to come by, as these antibodies are in wide use today as cancer treatments. Adding such antibodies to the mix substantially restored T cells' erstwhile-diminished responsiveness to the patients' shingles-virus-primed macrophages.

Disabling the ability of the patients' macrophages to metabolize sugar likewise restored their capacity to incite T cell action. In particular, a small-molecule compound called ML265, which is now in clinical cancer trials, largely reversed PD-L1 overexpression on the surface of patients' macrophages.

Just what makes macrophages go crazy for sugar in the first place is still an open question, Weyand said. But, she noted, the defect shows up in monocytes before they take up residence in tissues and mature into macrophages. "Finding out why this happens is the next frontier," she said. But the new findings of the current study could lead to earlier detection and treatment of coronary artery disease.

Other co-authors of the study are postdoctoral scholars Hong Namkoong, PhD, and Hui Zhang, MD; medical student Benedikt Schaefgen; Gerald Berry, MD, professor of pathology; Jennifer Tremmel, MD, assistant professor of cardiovascular medicine; John Giacomini, MD, professor of cardiovascular medicine at the Veterans Affairs Palo Alto Health Care System; and Jorg Goronzy, MD, professor of immunology and rheumatology.

Scientists from Vanderbilt University also helped carry out the study.

The study was funded by the National Institutes of Health and the Cahill Discovery Fund.

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

Scientists turbocharge microscope-quality 3-D imaging

By Bruce Goldman

You may not have heard of optical coherence tomography, or OCT. But if you've visited an ophthalmologist recently, chances are your eye came within an inch or two of a scanning device employing the technology. Tens of thousands of these devices are in place in doctors' offices, where they're widely used to check for eye diseases.

Now, Stanford scientists have figured out how to retrofit these high-performance machines with off-the-shelf components, increasing OCT's resolution by several-fold and promising earlier detection of retinal and corneal damage, incipient tumors and more.

The relatively simple, low-cost fix — entailing a pair of lenses, a piece of ground glass and some software tweaks — erases blemishes that have bedeviled images obtained via OCT since its invention in 1991. This improvement, combined with the technology's ability to optically penetrate up to 2 millimeters into tissue, could enable physicians to perform "virtual biopsies," visualizing tissue in three dimensions at microscope-quality resolution without excising any tissue from patients.

In a study published online June 20 in *Nature Communications*, the researchers tested the enhancement in two different commercially available OCT devices. They were able to view cell-scale features in intact tissues, including in a living mouse's ear and a human fingertip, said the study's senior author, Adam de la Zerda, PhD, assistant professor of structural biology. The study's lead author is electrical-engineering graduate student Orly Liba.

Boosting resolution

"We showed that you can take effectively any OCT system out there and, with minimal changes, boost its resolution to the point where it can detect anatomical features smaller than the size of a typical cell," de la Zerda said.

OCT is a billion-dollar business. Every year, more than 10 million OCT scans are performed to diagnose or monitor conditions from age-related macular degeneration to melanoma. The technology has been adapted for endoscopic use in pulmonary, gastrointestinal and cardiovascular medicine.

Somewhat analogous to ultrasound, OCT penetrates tissues optically instead of with sound waves. The device aims beams of laser light at an object — say, a tissue sample, or a patient's eye — and records what comes back when light bounces off reflective elements within the sample or eyeball. Adjusting the depth of penetration, a user can scan layer upon layer of a tissue and, piling virtual slices of tissue atop one another, assemble them to generate a volumetric image.

But to this day, OCT continues to be plagued by a form of noise that, unlike the random noise generated by any sensing system, can't be "washed away" simply by repeatedly imaging the object of interest and averaging the results with a computer program.

The noise generated by OCT, called "speckle," is an inherent feature of the architecture of the object being viewed and the unique properties of laser light.

A photon isn't a mere particle. It's also a wave whose power waxes and wanes as it travels, similar to an ocean wave heading toward the shore. When two waves collide, their combined height at the moment of their collision depends on whether each was at its peak, its trough or somewhere in between.

When photons get out of phase

The photons comprising a beam of laser light are in phase: They share the same wavelength, with their peaks and troughs occurring in sync. But when these photons bounce off of two separate surfaces — say, two closely situated components of a cell — the length of their return routes differs slightly, so they're no longer in phase. Now, they can interfere with one another just like intersecting ocean waves. They may cancel each other out, creating a false-black speckle on the resulting image. Or they may reinforce one another, creating a false-white speckle. If the speckle-generating components' positions are fixed, as is the case in most tissues (circulating blood being one exception), those same speckles will pop up in the same places on every successive OCT scan.

"Other researchers have tried various fixes, such as scanning repeatedly at different angles or from consecutive adjacent positions or with shifting wavelengths, or 'removing' the speckles using computer post-processing," de la Zerda said. "But the result is always the same: a blurred image." It's like covering up freckles with a coat of makeup: a smoother appearance, at the cost of lost detail.

NORBERT VON DER GROEBEN

Adam de la Zerda and his team have devised a way to improve the quality of images obtained through optical coherence tomography.

In principle, if you could reach in with a molecular tweezers and move one of those two interfering components just a tiny bit, you would change the speckle pattern. But you can't. However, the Stanford scientists found a way to do essentially the same thing, optically speaking.

"We wanted to make the speckles dance, so they'd be in a slightly different pattern each time we scanned the tissue," Liba said. "And we found a way to do it."

Creating a virtual image

By positioning a couple of additional lenses in the OCT device's line of sight, the investigators were able to create a second image — a holograph-like exact lookalike of the viewed sample that appeared elsewhere along the line of sight, between the added lenses and the sample. By inserting what they call a "diffuser" — a plate of glass they'd had roughened by randomly etching tiny grooves into it — at just the right point in the line of sight and methodically moving it between each round of repeated scans, they achieved the optical equivalent of shifting the geographical relationship of the sample's components just a tiny bit each time they scanned it.

Now, averaging the successive images removed the speckles. The Stanford team used the resulting enhanced capability to acquire detailed, essentially noise-free images of a living, anesthetized mouse's ear.

"We saw sebaceous glands, hair follicles, blood vessels, lymph vessels and more," Liba said.

They also obtained high-resolution images of a mouse retina and cornea. And an incision-free look at the fingertip of one of the study's co-authors let them see an anatomical feature never before glimpsed with OCT: Meissner's corpuscle, a nerve bundle responsible for tactile sensations.

The technological advance gets around a 25-year-old problem that has persistently limited OCT's diagnostic capabilities, de la Zerda said.

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.

De la Zerda is a member of the Stanford Cancer Institute and of Stanford Bio-X and is a Chan-Zuckerberg Biohub investigator. Liba is a Bio-X fellow.

Stanford's Office of Technology Licensing has applied for patents on intellectual property associated with the findings in the study.

Other Stanford co-authors of the study are former postdoctoral scholars Matthew Lew, PhD, and Debasish Sen, PhD; graduate student Elliott SoRelle; research assistant Rebecca Dutta; professor of ophthalmology Darius Moshfeghi, MD; and professor of physics and of molecular and cellular physiology Steven Chu, PhD.

The work was funded by the National Institutes of Health, the National Science Foundation, the U.S. Air Force, the Claire Giannini Fund, the Damon Runyon Cancer Research Foundation, the Susan G. Komen Foundation, the Mary Kay Foundation, the Donald E. and Delia B. Baxter Foundation, the Skippy Frank Foundation, the Center for Cancer Nanotechnology Excellence and Translation, and Stanford Bio-X.

Stanford's Department of Structural Biology also supported the work. ISM

For the first time, long-read genome sequencing used with patient

By Emma Hiolski

When Ricky Ramon was 7, he went for a routine checkup. The pediatrician, who lingered over his heartbeat, sent him for a chest X-ray, which revealed a benign tumor in the top-left chamber of his heart. For Ramon, it was the beginning of a long series of medical appointments, procedures and surgeries that would span nearly two decades.

During this time, noncancerous tumors kept reappearing in Ramon's heart and throughout his body — in his pituitary gland, adrenal glands above his kidneys, nodules in his thyroid.

The trouble was, doctors couldn't diagnose his condition.

When Ramon was 18, doctors thought his symptoms were suggestive of Carney complex, a genetic condition caused by mutations in a gene called PRKAR1A. However, evaluation of Ramon's DNA revealed no disease-causing variations in this gene.

Now, eight years later, researchers at the School of Medicine have used a next-generation technology — long-read sequencing — to secure a diagnosis for Ramon. It's the first time long-read, whole-genome sequencing has been used in a clinical setting, the researchers report in a paper published online June 15 in *Genetics in Medicine*.

Genome sequencing involves snipping DNA into pieces, reading the fragments, and then using a computer to patch the sequence together. DNA carries our genetic blueprint in a double-stranded string of molecular "letters" called nucleotides, or base pairs. The four types of nucleotides are each represented by a letter — C for cytosine and G for guanine, for example — and they form links across the two strands to hold DNA together.

'Illuminating a dark corner'

Current sequencing technologies cut DNA into "words" that are about 100 base-pairs, or letters, long, according to the study's senior author, Euan Ashley, DPhil, FRCP, professor of cardiovascular medicine, of genetics and of biomedical data science. Long-read sequencing, by comparison, cuts DNA into words that are thousands of letters long.

"This allows us to illuminate dark corners of the genome like never before," Ashley said. "Technology is such a powerful force in medicine. It's mind-blowing that we are able to routinely sequence patients' genomes when just a few years ago this was unthinkable."

The study was conducted in collaboration with Pacific Biosciences, a biotechnology company in Menlo Park, California, that has pioneered a type of long-read sequencing. Lead authorship of the paper is shared by Jason Merker, MD, PhD, assistant professor of pathology and co-director of the Stanford Clinical Genomics Service, and Aaron Wenger, PhD, of Pacific Biosciences.

The type of long-read sequencing developed by the research team's collaborators at Pacific Biosciences can continuously spool long threads of DNA for letter-by-letter analysis, limiting the number of cuts needed.

"This is exciting," said Ashley, "because instead of having 100-base-pair 'words,' you now have 7,000- to 8,000-letter words."

Falling cost

Thanks to technological advances and increased efficiency, the cost of long-read sequencing has been falling dramatically. Ashley estimated the current cost of the sequencing used for this study at between $5,000 and $6,000 per genome.

Though the cost of short-read sequencing is now below $1,000, according to Ashley, parts of the genome are not accessible when cutting DNA into small fragments. Throughout the genome, series of repeated letters, such as GGCGGCGGC, can stretch for hundreds of base pairs. With only 100-letter words, it is impossible to know how long these stretches are, and the length can critically determine someone's predisposition to disease.

Additionally, some portions of the human genome are redundant, meaning there are multiple places a 100-base pair segment could potentially fit in, said Ashley. This makes it impossible to know where to place those segments when reassembling the genome. With longer words, that happens much less often.

Given these issues,

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OBITUARY

Professor emeritus of surgery Thomas Nelsen dies at 90

By Tracie White

Thomas Nelsen, a professor emeritus of surgery at the School of Medicine whose research contributed to the university's life-saving advances in the treatment of Hodgkin's lymphoma, died March 17 in Idaho surrounded by family and friends. He was 90.

His dog, Martine, a constant companion, died just a few days before him in California while Nelsen was staying at a family vacation home in Sun Valley, said his daughter Karen Nelsen.

Nelsen, who came to Stanford in 1960 from the University of Chicago, became a member of Stanford's world-renowned Hodgkin's lymphoma program back when the concept of radiation treatment for cancer was in its infancy. He conducted diagnostic surgical procedures during clinical trials that helped radiotherapists pinpoint exactly where to target the experimental radiation treatments from a linear accelerator designed for medical use.

These new treatments were pioneered in 1962 by two Stanford faculty members — radiologist Henry Kaplan, MD, and oncologist Saul Rosenberg, MD — who conducted the clinical trials that eventually transformed the once-fatal disease into a curable one.

"He was a great surgeon from Chicago who was important in our Hodgkin's studies," said Rosenberg, professor emeritus of oncology.

"I've always considered him a pioneer," said John Schroeder, MD, professor of cardiovascular medicine at Stanford, who became Nelsen's friend and cardiologist. "I still see patients in my practice who at age 20 received radiation therapy at Stanford and now are in their 70s or 80s."

Development of surgical lasers

After retiring from Stanford in 1988, Nelsen worked on the development of surgical lasers, in particular the holmium laser, and served as a board member and adviser on medical lasers at Coherent Inc. into the late 1990s, according to Karen Nelsen.

Thomas Nelsen

When his eyesight began to decline late in life due to macular degeneration, he took to driving a three-wheeled electrical bicycle to the hospital and the grocery store to maintain his independence, and rigged up a video system at home that allowed him to use his large-screen television as a reading device, she said.

"He was very bright and had a great sense of humor," Schroeder said. "He continued to cross-country ski until last year, always challenging me to ski with him."

Born in 1926, Nelsen grew up in Tacoma, Washington. His father was a surgeon who also kept racehorses. Nelsen graduated early from Stadium High School and enrolled at Harvard University in 1943. He married Shirley Polson, his childhood sweetheart, in 1945, immediately after the end of World War II. Together, the two transferred — Nelsen from Harvard and Polson from Vassar — first to UCLA and then to the University of Washington, where Nelsen graduated with a degree in zoology in 1947.

Military service and academia

He earned a medical degree from the University of Washington in 1951 and completed an internship and residency at the University of Chicago. His education was interrupted by military service in the early 1950s during the Korean War. In 1959, he became an assistant professor at Chicago.

Always active, he had many interests, including going to the opera, duck hunting and piloting airplanes. He traveled in Europe and Japan and also took an interest in photography.

After the death of his first wife in 1979, Nelsen married Roselyne Lombard, in 1981, a French nuclear physicist who participated in research at the Stanford Linear Accelerator Center. After his retirement, the two divided their time between a home on the Stanford campus, the home in Sun Valley and a home in Paris.

Nelsen was a member of the Institute for Electrical and Electronics Engineers, as well as several surgical societies.

He is survived by his wife, Roselyne Lombard Nelsen; his daughters Karen Nelsen of Berkeley and Roxanne Nelsen of Los Altos; and his granddaughter.

For information about a memorial planned for late July contact Karen Nelsen at (510) 912-8681. ISM

Sequencing

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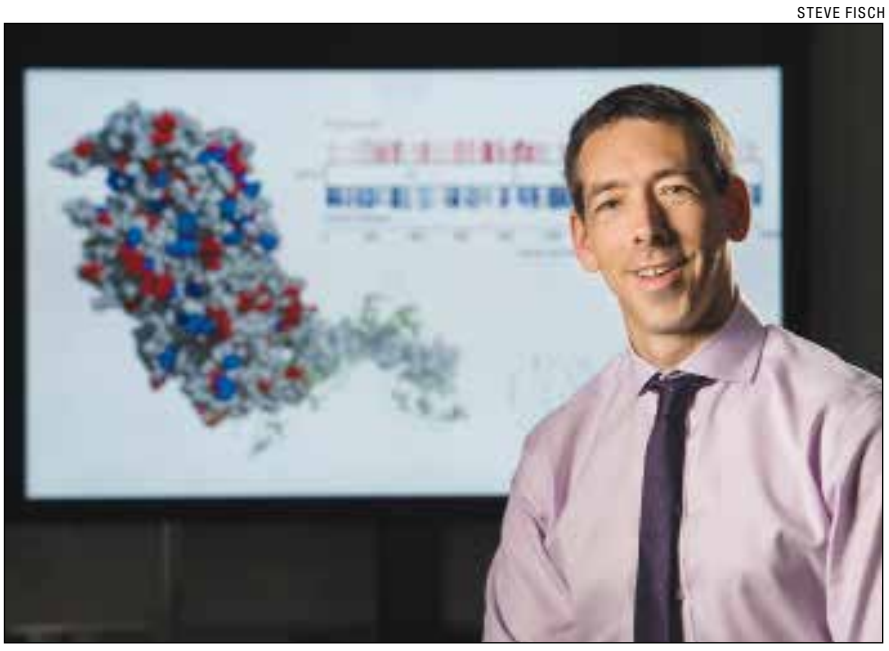
5 percent of the genome cannot be uniquely mapped, the researchers wrote. And any deletions or insertions longer than about 50 letters are too long to detect.

For patients with undiagnosed conditions, short-read sequencing can help doctors provide a diagnosis in about one-third of cases, said Ashley. But Ramon's case was not one of those.

The technique initially used to analyze Ramon's genes failed to identify a mutation in the gene responsible for Carney complex, though Ashley said co-author Tam Sneddon, DPhil, a clinical data scientist at Stanford Health Care who browsed through the database of Ramon's sequenced genome by hand, did notice something looked wrong. Ultimately, the long-read sequencing of Ramon's genome identified a deletion of about 2,200 base-pairs and confirmed that a diagnosis of Carney complex was indeed correct.

STEVE FISCH



Euan Ashley and his collaborators used long-read genome sequencing to diagnose a rare condition in a patient. It's the first time the technique has been used in a clinical setting.

This 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.

An 'exceedingly rare' condition

Carney complex arises from mutations in the PRKAR1A gene, and is characterized by increased risk for several tumor types, particularly in the heart and hormone-producing glands, such as ovaries, testes, adrenal glands, pituitary gland and thyroid. According to the National Institutes of Health, fewer than 750 individuals with this condition have been identified.

The most common symptom is benign heart tumors, or myxomas. Open heart surgery is required to remove cardiac myxomas; by the time Ramon was 18 years old, he'd had three such surgeries. He is under consideration for a heart transplant, and having the correct diagnosis for his condition was important for the transplant team. Beyond the typical screening for a transplant, Ashley said the team needed to ensure there weren't other health issues that could be exacerbated by immune suppressants, which heart transplant patients must take to avoid rejection of the donated organ.

Though it helps his medical team to have a confirmed diagnosis of Carney complex, Ramon has found it disheartening to face the fact that he cannot escape his condition. "I was pretty sad," he said. "It took me a while to come to terms with the fact that I'll have this until the day I die."

He tries not to dwell on it, though. "Live one day at a time," he said. "The bad days are temporary storms, and they'll pass."

"His story is quite incredible," said Ashley, who said it was a privilege to be working on Ramon's team. "To have such a burden on such young shoulders, and to decide whether or not he wants a transplant, requires incredible courage."

Because he couldn't wait any longer for a transplant, Ramon recently underwent his fourth surgery to remove three tumors in his heart. JosephWoo, MD, professor and chair of cardiothoracic surgery at Stanford, performed the operation. "It is exceedingly rare to have tumors in the heart," said Ashley. "It was a particularly heroic operation." Though Ramon is still under consideration for a transplant, the need is less urgent now.

"I'm in good hands," Ramon said of the Stanford team. "I'm glad to be here."

A future in the clinic?

Ashley said he and many other doctors believe that long-read technology is part of the future of genomics.

"Now we get to see how to do it better," said Ashley. "If we can get the cost of long-read sequencing down to where it's accessible for everyone, I think it will be very useful."

Other Stanford co-authors of the study are genetic counselor Megan Grove; former graduate student Zach Zappala, PhD; postdoctoral scholar Laure Fresard, PhD; senior research engineer Daryl Waggott, MSc; Sowmi Utiramerur, MS, director of bioinformatics for Stanford's Clinical Genomics Service; research assistant Yanli Hou, PhD; research scientist Kevin Smith, PhD; Stephen Montgomery, PhD, assistant professor of pathology and of genetics; Matthew Wheeler, MD, PhD, clinical assistant professor of cardiovascular medicine; Jillian Buchan, PhD, clinical assistant professor of pathology; and James Ford, MD, professor of medicine and of genetics.

Pacific Biosciences paid for the sequencing.

Stanford's Department of Pathology and the Stanford Cancer Institute also supported the work. ISM

Center for Digital Health awards grants, 1,000 Apple Watches

The Stanford Center for Digital Health has awarded five seed grants and a total of 1,000 Apple Watches to research projects led by Stanford faculty.

The projects are designed to study whether creative uses of the smartwatches can achieve meaningful health care outcomes.

The center aims to advance the field of digital health by enabling research collaborations between faculty members and technology companies.

"Our goal, simply stated, is to enable the Stanford community to do cool stuff to improve health care with technology," said Mintu Turakhia, MD, associate professor of cardiovascular medicine and senior director of research and innovation at the center.

The center provides platforms for digital health experts, industry members and students to come together and share knowledge; it's also an internal resource for the Stanford community, providing infrastructure and support in the field of digital health.

"We aim to facilitate novel and transformative research with health care technology, leveraging the expertise and academic rigor of Stanford," said Lauren Cheung, MD, MBA, clinical assistant professor of medicine and senior director of strategy and operations at the center.

Following is a list of the projects that received seed funding and their principal investigators:

- Harnessing mindset in health technology — Alia Crum, PhD, assistant professor of psychology.
- ReClaim: A virtual therapist for stroke patient arm recovery — Maarten Lansberg, MD, PhD, associate professor of neurology and neurological sciences; Scott Delp, PhD, professor of bioengineering and of mechanical engineering; and Kara Flavin, MD, clinical assistant professor of orthopaedic surgery and of neurology and neurological sciences.
- Exploring an artificial intelligence approach to support adherence behaviors in psychiatric clinical care — Sarah Adler, PsyD, clinical assistant professor of psychiatry and behavioral sciences, and Jane Kim, PhD, instructor of psychiatry and behavioral sciences.
- Stop, watch: Reducing hyperactivity and supporting attention for youth with ADHD — Leanne Williams, PhD, professor of psychiatry and behavioral sciences
- Individualized migraine attack prediction with self-reported and passively collected data — Lorene Nelson, PhD, assistant professor of health research and policy. ISM

Graduation

continued from page 1

PHOTOS BY STEVE FISCH

Augustus White (left), who earned an MD from Stanford in 1961, addressed graduating students (right), urging them to help mend the nation's health care system.

graduation. "I don't feel like a real doctor yet. I'm still letting it sink in."

Looking back, looking ahead

She and three of her closest friends in medical school huddled together, laughing over memories of the camping trip they took during first-year orientation and already planning for future reunions as they head off to different cities and states.

Graduate Tom Roberts, MD, MBA, lingered with his father, mother and two sisters just prior to the ceremony. He would have to dash off immediately after the ceremony to grab his second diploma at a cross-campus ceremony for Stanford MBA graduates.

"I was surprised he went into medicine," said his dad, Ken Roberts, beaming with pride. "He always said 'I'm not going into medicine,'" said his mother, Sheila Roberts. Tom said that Ken, a physician himself in the town of Mechanicsville, Virginia, where Tom grew up, set a good example for him.

The two student speakers — Zachary Zappala, who earned a PhD in genetics, and Monica Coughlan, who earned an MD — offered words of encouragement and congratulations to their fellow graduates.

Coughlan, who is headed to UC-San Francisco for a residency in orthopaedic surgery, thanked her patients for teaching her so much, including humility.

"Our hands were the first to hold a newborn baby as we delivered them to their mother," she said. "... We have easily worked with thousands of patients. Patients whose stories we will never forget."

Zappala discussed his worries about starting a career as a scientist in the current political climate but reassured his classmates.

"We are living in an unpredictable political climate where support for scientific research has become disturbingly partisan," he said. "In particular, our government seems to place little merit on scientific research as it proposed significant funding cuts of the National Institutes of Health, which has funded most of our education."

"It's important for us to rebuild public trust in science," he added. "You are well-equipped to tackle anything that comes your way, and I wish you all the best of luck." ISM

Members of Stanford Medicine community honored for teaching, patient care

Toward the end of spring quarter, nearly 40 faculty, staff members, residents and students were recognized with 2017 awards for outstanding contributions to Stanford Medicine.

Awards in medicine

Stephan Busque, MD, professor of surgery and director of the adult kidney and pancreas transplant program; Jeffrey Dunn, MD, clinical professor of neurology and neurological sciences and chief of clinical neuroimmunology; and Peter Pompei, MD, clinical professor of medicine, received the Arthur L. Bloomfield Award in Recognition of Excellence in the Teaching of Clinical Medicine.

Erika Schillinger, MD, clinical professor of medicine, received the Franklin G. Ebaugh, Jr. Award for Excellence in Advising Medical Students.

James Lau, MD, clinical associate professor of surgery, received the Alwin C. Rambar-James BD Mark Award for Excellence in Patient Care, which recognizes a member of the medical faculty for compassion in working with patients and their families, excellence in providing medical treatment, and effectiveness and pleasantness in interactions with patient-care staff.

Darren Salmi, MD, clinical assistant professor of surgery and of pathology, received the Lawrence H. Mathers Award for Exceptional Commitment to Teaching and Active Involvement in Medical School Education.

Sakti Srivastava, MD, associate professor of surgery, director of Digital MEdIC and chief of clinical anatomy, received the Award for Excellence in Promotion of the Learning Environment and Student Wellness.

Ray Jackman, advising coordinator, received the Medical Education Staff Service Award.

Vivek Bhalla, MD, assistant professor of medicine and director of the Stanford Hypertension Center, received the Outstanding Lecture/Presentation Award.

Suvarna Akki, MD, a physician at the Veterans Affairs Palo Alto Health Care System, received the Outstanding Community Clinic Preceptor, Preclinical Instruction Award.

Thomas Ormiston, MD, a physician at Santa Clara Valley Medical Center, received the Outstanding Community Clinical Preceptor, Clinical Instruction Award.

Samuel Rodriguez, MD, clinical assistant professor of anesthesiology, perioperative and pain medicine, received the Henry J. Kaiser Family Foundation Teaching Award for Outstanding and Innovative Contributions to Medical Education.

Manuel Amieva, MD, associate professor of pediatrics and of microbiology and immunology; Martin Bronk, MD, consulting associate professor of surgery; Sharon Chen, MD, clinical associate professor of pediatrics; and Andrew Nevins, MD, clinical associate professor of medicine, received the Henry J. Kaiser Family Foundation Award for Excellence in Preclinical Teaching.

Mehreen Iqbal, MD, resident in pediatrics; Eric Strong, MD, clinical assistant professor of medicine; and Grace Yu, MD, adjunct clinical assistant professor of medicine, received the Henry J. Kaiser Family Foundation Award for Excellence in Clinical Teaching.

Medical residents Collin Culberston, MD, neurology; Jessica Gold, MD, psychiatry; Kyle Graham, MD, obstetrics and gynecology; Andre Kumar, MD, medicine; Lindsay Sceats, MD, surgery; and Charlie Wickremasinghe, MD, pediatrics, received the Arnold P. Gold Foundation Award for Humanism and Excellence in Teaching. The award is given to residents based on their commitment to teaching and the compassionate treatment of students, colleagues and patients and their families.

Carlie Arbaugh, a medical student, received the Teaching Assistant Award.

Neil Gesundheit, MD, professor of medicine and associate dean for academic advising; Lars Osterberg, MD, associate professor of medicine; and Yasmin Owusu, MD, clinical assistant professor of psychiatry and behavioral sciences, received the Award for Excellence in Promotion of Humanism.

Cesar Lopez Angel, a medical student, received the Award for Excellence in Promotion of Diversity and Society Citizenship.

Medical students inducted into the Gold Humanism Honor Society include Alexander Fogel, Madeline Grade, Julia Jezmir, Ryosuke Kita (MD-PhD), Mythili Prabhu, Nitya Rajeshuni, Robyn Shaffer, Paula Trepman, Brandon Turner, Sarah Waliany, Nicholus Warstadt and Grace Xiong. Members of the society, organized by the Arnold P. Gold Foundation, are selected for exemplifying compassionate patient care and serving as role models, mentors and leaders.

Awards in bioscience

Jennifer Raymond, PhD, professor of neurobiology, received the Award for Excellence in Graduate Teaching. The award recognizes faculty whose teaching of graduate students is distinguished and especially valued by the medical school's biosciences community.

Steven Bagley, MD, executive director of the Biomedical Informatics Training Program, received the Award for Excellence in Diversity and Inclusion. This award recognizes faculty and academic staff who make distinguished contributions toward enhancing diversity, equity and inclusion in the biosciences.

Marion Buckwalter, MD, PhD, associate professor of neurosurgery and of neurology and neurological sciences, received the Award for Excellence in Mentoring and Service. This award recognizes faculty who make distinguished contributions toward enhancing the quality of training and the educational experience for biosciences graduate students. ISM

New website offers employees information on campus resources, news and events

By Kris Newby

The School of Medicine has launched a new community website designed to inform and enrich the lives of the people who work for the school.

Called Stanford Medicine Connected, the website will make it easier for employees to find resources, news, cultural events and classes across the university.

The project was launched last June by Marcia Cohen, senior associate dean for finance and administration, in response to the school's 2015 engagement survey, which found that employees wanted a better way to stay informed about campus happenings.

The project started with an analysis of past and present employee information resources, including the school's Local Users' Home Page, a webpage of useful links launched about a decade ago. Then Marianne Bishop, a project manager for Information Resources & Technology, organized focus groups with faculty, staff and students to help shape the content.

A SUNet ID is necessary to get access to "Connected," which can serve as a forum for internal campus news and employee kudos. Employee submissions and suggestions are encouraged. The site is also the first to use One Directory, a contact database that seamlessly enables users to search for employee contact information across the university and its affiliated hospitals.

In addition, the new site is designed to work well on mobile devices and is compatible with emerging hearing- and sight-impaired accessibility requirements.

To try out Connected, visit http://med.stanford.edu/connected.html ISM

Ribosomes

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of the study, which was published online June 15 in *Molecular Cell.* Postdoctoral scholars Zhen Shi, PhD, and Kotaro Fujii, PhD, share lead authorship. Barna is a New York Stem Cell Robertson Investigator and is also a member of Stanford's Bio-X and Child Health Research Institute.

The work builds upon a previous study from Barna's laboratory that was published June 1 in *Cell*. The lead author of that study was postdoctoral scholar Deniz Simsek, PhD. It showed that ribosomes also differ in the types of proteins they accumulate on their outer shells. It also identified more than 400 ribosome-associated proteins, called RAPs, and showed that they can affect ribosomal function.

Every biology student learns the basics of how the genetic code is used to govern cellular life. In broad strokes, the DNA in the nucleus carries the building instructions for about 20,000 genes. Genes are chosen for expression by proteins that land on the DNA and "transcribe" the DNA sequence into short pieces of mobile, or messenger, RNA that can leave the nucleus. Once in the cell's cytoplasm, the RNA binds to ribosomes to be translated into strings of amino acids known as proteins.

Every living cell has up to 10 million ribosomes floating in its cellular soup. These tiny engines are themselves complex structures that contain up to 80 individual core proteins and four RNA molecules. Each ribosome has two main subunits: one that binds to and "reads" the RNA molecule to be translated, and another that assembles the protein based on the RNA blueprint. As shown for the first time in the *Cell* study, ribosomes also collect associated proteins called RAPs that decorate their outer shell like Christmas tree ornaments.

'Hints of a more complex scenario'

"Until recently, ribosomes have been thought to take an important but backstage role in the cell, just taking in and blindly translating the genetic code," said Barna. "But in the past couple of years there have been some intriguing hints of a more complex scenario. Some human genetic diseases caused by mutations in ribosomal proteins affect only specific organs or tissues, for example. This has been very perplexing. We wanted to revisit the textbook notion that all ribosomes are the same."

In 2011, members of Barna's lab showed that one core ribosomal protein called RPL38/eL38 is necessary for the appropriate patterning of the mammalian body plan during development; mice with a mutation in this protein developed skeletal defects such as extra ribs, facial clefts and abnormally short, malformed tails.

Shi and Fujii used a quantitative proteomics technology called selected reaction monitoring to precisely calculate the quantities, or stoichiometry, of each of several ribosomal proteins isolated from ribosomes within mouse embryonic stem cells. Their calculations showed that not all the ribosomal proteins were always present in the same amount. In other words, the ribosomes differed from one another in their compositions.

"We realized for the first time that, in terms of the exact stoichiometry of these proteins, there are significant differences among individual ribosomes,"

NORBERT VON DER GROEBEN

Maria Barna and her team found that ribosomes have the ability to regulate genes — an unexpected finding that may challenge scientists to rethink their understanding of gene regulation.

said Barna. "But what does this mean when it comes to thinking about fundamental aspects of a cell, how it functions?"

To find out, the researchers tagged the different ribosomal proteins and used them to isolate RNA molecules in the act of being translated by the ribosome. The results were unlike what they could have ever imagined.

"We found that, if you compare two populations of ribosomes, they exhibit a preference for translating certain types of genes," said Shi. "One prefers to translate genes associated with cell metabolism; another is more likely to be translating genes that make proteins necessary for embryonic development. We found entire biological pathways represented by the translational preferences of specific ribosomes. It's like the ribosomes have some kind of ingrained knowledge as to what genes they prefer to translate into proteins."

The findings dovetail with those of the *Cell* paper. That paper "showed that there is more to ribosomes than the 80 core proteins," said Simsek. "We identified hundreds of RAPs as components of the cell cycle, energy metabolism, and cell signaling. We believe these RAPs may allow the ribosomes to participate more dynamically in these intricate cellular functions."

Cells freed from micromanaging gene expression

The fact that ribosomes can differ among their core protein components as well as among their associated proteins, the RAPs, and that these differences can significantly affect ribosomal function, highlights a way that a cell could transform its protein landscape by simply modifying ribosomes so that they prefer to translate one type of gene — say, those involved in metabolism — over others. This possibility would free the cell from having to micromanage the expression levels of hundreds or thousands of genes involved in individual pathways. In this scenario, many more messenger RNAs could be available than get translated into proteins, simply based on what the majority of ribosomes prefer, and this preference could be tuned by a change in expression of just a few ribosomal proteins.

Although the findings of the two papers introduce a new concept of genetic regulation within the cell, they make a kind of sense, the researchers said.

"About 60 percent of a cell's energy is spent making and maintaining ribosomes," said Barna. "The idea that they play no role in the regulation of genetic expression is, in retrospect, a bit silly."

Other Stanford co-authors are graduate students Kyle Kovary and Naomi Genuth; postdoctoral scholar Hannes Rost, PhD; and Mary Teruel, PhD, assistant professor of chemical and systems biology.

The research was supported by the New York Stem Cell Foundation, the Alfred P. Sloan Foundation, the Mallinckrodt Foundation, a Pew Scholars Award and the National Institutes of Health.

Stanford's departments of Developmental Biology and of Genetics also supported the work. ISM

Muscle

continued from page 1

animals' ability to repair the damage and regain muscle strength, the researchers reported.

However, a nonsteroidal, anti-inflammatory drug like aspirin or ibuprofen blocked production of the metabolite and dramatically inhibited muscle repair in the mice, leading to diminished strength.

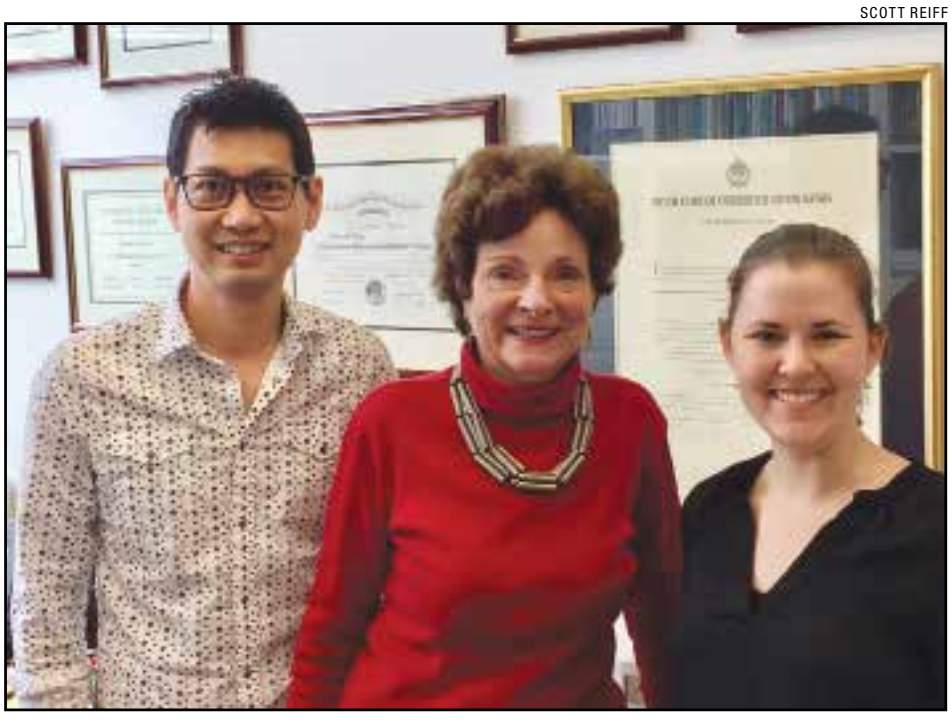
"Traditionally, inflammation has been considered a natural, but sometimes harmful, response to injury," said Helen Blau, PhD, professor of microbiology and immunology and director of Stanford's Baxter Laboratory for Stem Cell Biology. "But we wondered whether there might be a component in the pro-inflammatory signaling cascade that also stimulated muscle repair. We found that a single exposure to prostaglandin E2 has a profound effect on the proliferation of muscle stem cells in living animals. We postulated that we could enhance muscle regeneration by simply augmenting this natural physiological process in existing stem cells already located along the muscle fiber."

A paper describing the research was published online June 12 in the *Proceedings of the National Academy of Sciences*. Blau, who holds the Donald E. and Delia B. Baxter Professorship, is the senior author. Senior scientist Andrew Ho and postdoctoral scholar Adelaida Palla share lead authorship of the study.

Metabolite infiltrates muscle fiber

Muscle stem cells usually nestle quietly along the muscle fibers. They spring into action when a muscle is damaged by trauma or overuse, dividing rapidly to generate enough muscle cells to repair the injury. But it's not entirely clear what signals present in inflammation activate the stem cells.

SCOTT REIFF



Andrew Ho, Helen Blau and Adelaida Palla led a study that found drugs like aspirin and ibuprofen can inhibit the ability of muscle tissue to repair itself in mice.

Prostaglandin E2, or PGE2, is a metabolite produced by immune cells that infiltrate the muscle fiber as well by the muscle tissue itself in response to injury. Anti-inflammatory treatments have been shown to adversely affect muscle recovery, but because they affect many different pathways, it's been tough to identify who the real players are in muscle regeneration.

Ho and Palla discovered a role for PGE2 in muscle repair by noting that its receptor was expressed at higher levels on stem cells shortly after injury. They found that muscle stem cells that had undergone injury displayed an increase in the expression of a gene encoding for a receptor called EP4, which binds to PGE2. Furthermore, they showed that the levels of PGE2 in the muscle tissue increased dramatically within a three-day period after injury, indicating it is a transient, naturally occurring immune modulator.

To determine its mechanism of action, Ho and Palla created a genetically engineered strain of laboratory mice that allowed them to dynamically monitor the number and activities of muscle stem cells over time. They then studied how the stem cells responded to leg muscle injuries caused by injection of a toxin or by application of cold temperatures. (The mice were anesthetized during the procedure and given pain relief during recovery.)

'We saw a profound effect'

"This transient pulse of PGE2 is a natural response to injury," said Blau. "When we tested the effect of a one-day exposure to PGE2 on muscle stem cells growing in culture, we saw a profound effect on the proliferation of the cells. One week after a single one-day exposure, the number of cells had increased sixfold compared with controls."

After seeing what happened in laboratory-grown cells, Ho and Palla tested the effect of a single injection of PGE2 into the legs of the mice after injury.

"When we gave mice a single shot of PGE2 directly to the muscle, it robustly affected muscle regeneration and even increased strength," said Palla. "Conversely, if we inhibited the ability of the muscle stem cells to respond to naturally produced PGE2 by blocking the expression of EP4 or by giving them a single dose of a nonsteroidal anti-inflammatory drug to suppress PGE2 production, the acquisition of strength was impeded."

"We are excited about this finding because it is counterintuitive," said Ho. "One pulse of this inflammation-associated metabolite lingers long enough to significantly affect muscle stem cell function in these animals. This could be a natural way to clinically boost muscle regeneration."

The researchers next plan to test the effect of PGE2 on human muscle stem cells in the laboratory, and to study whether and how aging affects the stem cells' response.

Other Stanford authors are former technician Matthew Blake; graduate student Nora Yucel; postdoctoral Yu Xin Wang, PhD; former graduate student Klas Magnusson, PhD; research associate Colin Holbrook; research assistant and lab manager Peggy Kraft; and Scott Delp, PhD, professor of bioengineering, of mechanical engineering and of orthopaedic surgery.

The study was supported by the Muscular Dystrophy Association, the Baxter Foundation, the California Institute for Regenerative Medicine and the National Institutes of Health.

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

PEOPLE

Tait Shanafelt appointed to lead center for physician well-being

By Ruthann Richter

Tait Shanafelt, MD, a nationally recognized expert in physician wellness, will join Stanford Medicine as its first chief wellness officer, effective Sept. 1, leading the medical center's pioneering program in the field.

His appointment makes Stanford the first academic medical center in the country to create a position of chief wellness officer at a time when physician burnout nationally has reached an all-time high. Shanafelt, whose clinical work and research focus on the treatment of patients with chronic lymphocytic leukemia, will direct the WellMD Center at Stanford Medicine and serve as associate dean of the School of Medicine.

He comes from the Mayo Clinic, where he led a successful initiative to counter burnout and improve physicians' sense of fulfillment and well-being.

"I am delighted to welcome Tait, who is an international thought leader and researcher in the field of physician wellness and its implications on quality of care," said Lloyd Minor, MD, dean of the School of Medicine. "He brings an unmatched set of accomplishments and capabilities to these new roles and an inspiring vision to firmly establish Stanford Medicine as the national leader in physician wellness."

Leading the way

Shanafelt has literally led the way in the field. Since 2008, he has overseen multiple national surveys that included more than 30,000 U.S. physicians and about 9,000 U.S. workers in other fields. These found increasing rates of burnout among doctors; in 2014, more than half of those surveyed were suffering from emotional exhaustion, loss of meaning in work and/or a sense of ineffectiveness and a lack of engagement with patients. Moreover, his studies have found that as physicians suffer, so do patients: Burnout has been found to contribute to physician errors, higher mortality among hospitalized patients and less compassionate care. It is a trend, he said, that is "eroding the soul of medicine."

"I think most health care leaders now realize this is a threat to their organization, but there is also uncertainty that they can do anything effective to address it," Shanafelt said. "They say, 'It's a national epidemic, what can we do?' My experience has shown that an individual organization that is committed to this at the highest level of leadership and that invests in well-designed interventions can move the needle and run counter to the national trend of physician distress and burnout. I hope that the Stanford WellMD Center becomes a paragon that other medical centers want to emulate."

Tait Shanafelt

Declining burnout rates at Mayo

As director of the Department of Medicine Program on Physician Well-Being at the Mayo Clinic, Shanafelt launched an effort to address physician distress through programs promoting physician autonomy, efficiency, collegiality and a sense of community. While many were focused on strategies to make individual physicians more resilient, Shanafelt and his team focused on systems, the practice environment, organizational culture, and leadership. As a result, the absolute burnout rates among Mayo physicians declined 7 percent over two years, despite an 11 percent rise in the rate among physicians nationally using identical metrics, surveys showed. A more recent assessment found the burnout rate among Mayo physicians was about two-thirds that of physicians nationally.

Shanafelt plans to work in collaboration with his new colleagues at Stanford, building on its innovative WellMD Center, which was established in 2016. The center has engaged more than 200 physicians through programs focusing on peer support, stress reduction and ways to cultivate compassion and resilience, as well as a literature and a dinner series in which physicians explore the challenges and rewards of being a doctor. The center also aims to relieve some of the burden on physicians by improving efficiency and simplifying workplace systems, such as electronic medical records.

In October, Stanford will host the first American Conference on Physician Health, in San Francisco, co-sponsored by the American Medical Association and the Mayo Clinic.

Bryan Bohman, MD, the center's interim director, said the WellMD team has worked closely with Shanafelt over the past year on projects of mutual interest.

"All of us at the center have been struck by Tait's collaborative nature, his integrity, his warmth, his generosity of spirit and his work ethic," said Bohman, chief medical officer for Stanford's University Healthcare Alliance. "Both at Mayo and nationally — in the physician wellness community — Tait is seen as an inspiring and strong leader. We couldn't be happier that he will be guiding our future wellness work at Stanford."

David Entwistle, president and CEO of Stanford Health Care, and Christopher Dawes, president and CEO of Packard Children's Hospital and Stanford Children's Health, both expressed strong support for Shanafelt's appointment as the leader of Stanford Medicine's wellness effort.

In addition to his work in physician well-being, Shanafelt is an international expert in the treatment of chronic lymphocytic leukemia. He said he plans to continue his work on leukemia at Stanford, devoting about 30 percent of his time to clinical research and the care of patients with the disease. ISM

OF NOTE

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

LINDA BOXER, MD, PhD, professor of hematology, was appointed to the board of the California Institute for Regenerative Medicine, the state's stem cell agency. She is the vice dean of the School of Medicine and the Stanley McCormick Memorial Professor.

SCOTT BOYD, MD, PhD, was appointed associate professor of pathology, effective May 1. His research examines B-cell and T-cell antigen receptors and genotype-phenotype relationships in healthy immune systems and in those affected by disease.

AIDA HABTEZION, MD, was promoted to associate professor of medicine, effective May 1. She is the Ballinger-Swindells Family Scholar. Her research focuses on leukocyte recruitment and immune responses in diseases of digestive organs.

MICHAEL Z. LIN, MD, PhD, was promoted to associate professor of neurobiology and of bioengineering, effective May 1. His research focuses on engineering proteins to visualize and control biochemical processes.

HOLDEN MAECKER, PhD, was promoted to professor (research) of microbiology and immunology, effective May 1. He directs the Human Immune Monitoring Center. His research is focused on T-cell responses to pathogens and cancer and on indicators of immune competence.

GARY STEINBERG, MD, PhD, professor and chair of neurosurgery, was awarded the 2017 H. Richard Winn, MD, Prize by the Society of Neurological Surgeons. The international award recognizes a neurological surgeon who has made and continues to make substantial contributions to clinical or basic neuroscience. It is the society's highest honor. Steinberg holds the Bernard and Ronni Lacroute-William Randolph Hearst Professorship in Neurosurgery and Neurosciences.

MATTHEW STREHLOW, MD, was appointed associate professor of emergency medicine, effective May 1. He directs Stanford Emergency Medicine International and its international emergency medicine fellowship. His interests include emergency medicine in developing countries, cardiology and critical care. ISM

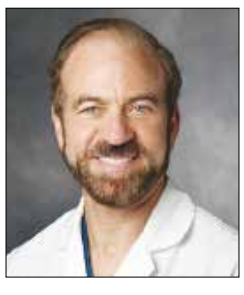
Linda Boxer

Scott Boyd

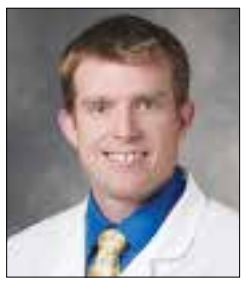
Aida Habtezion

Michael Lin

Holden Maecker



Gary Steinberg



Matthew Strehlow

Scientists receive Parker Institute awards

By Ruthann Richter

Two young investigators at the School of Medicine have received awards from the Parker Institute for Cancer Immunotherapy to advance their research and further their careers in the field of cancer immunotherapy.

Ansuman Satpathy, MD, PhD, a postdoctoral scholar and instructor in pathology, has been named a Parker Bridge Scholar. The award, which will provide him with $650,000 over a three-year period, will support his research in cancer immunology and epigenomics as he transitions into a faculty position at Stanford.

Zinaida Good, a graduate student in computational and systems immunology, has been named a Parker Scholar. She will receive $67,000 for a year, with the possibility of renewal for a second year, to help her move into a position as a postdoctoral scholar at Stanford and continue her work on refining engineered T-cell therapies for patients with cancer.

Ansuman Satpathy

Zinaida Good

The awards are designed to help train the next generation of scientists in cancer immunotherapy by supporting promising young researchers doing innovative work that has the potential for great impact. The Stanford investigators were among six from around the country receiving awards totaling $3.46 million.

"The Parker Institute has created a community of scientists working together to mobilize the immune system against cancer and improve patient outcomes. They have brought together some of the world's best scientists and created incentives for them to collaborate," Good said. "This is a real honor to become a part of this community. Discussing ideas with other researchers is really helpful in shaping research questions and thinking critically about your discoveries."

Using an advanced, single-cell analysis tool called cytometry by time-of-flight, she has created a high-resolution map of human T-cell differentiation and was able to "steer" T-cell fate towards a clinically useful phenotype. She plans to apply this approach to T cells engineered with chimeric antigen receptors, so these cells can effectively target cancer cells in patients and persist over time to prevent cancer from recurring.

Satpathy has been working in the lab of Howard Chang, MD, PhD, professor of dermatology, where he's been focusing on why cancer immunotherapy works well in some patients but not as well in others. He and his colleagues have developed new genome-sequencing methods to study how T cells function and undergo change in the presence of cancer.

In so doing, "We can see what is happening in patients that is working well and what is not, and incorporate those insights in order to design better therapies in the future," Satpathy said. Now a third-year resident in pathology, he will continue to work in Chang's lab while he transitions to being an independent investigator and faculty member.

"I think that transition is particularly difficult both in terms of funding and developing relationships with other scientists and collaborators," he said. "This award helps in both areas. It provides funding, but more importantly it provides membership in a community of scientists who are the best in cancer immunotherapy and immunology." ISM