Grads urged to promote health care equality

By Tracie White

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 graduates, dressed in caps and gowns, cousins and friends. With balloons and flowers, they cheered in support of the nearly 417 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 uncovered 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.

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 development biology and of genetics. “These findings will likely change the dogma for how the genetic code is translated. Until now, each of the 1 to 10 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

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.
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 re-searchers 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 functioning on distant 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, co-authored by J. Craig Venter, PhD, chair of the Institute for Personalized Medicine, and of biology, is the senior author. Graduate student Evan Boyle and postdoctoral scholar Yang Li, PhD, shared top 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 100 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 but have 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 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 complex 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.

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 uninformative 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 gives 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.”

The work 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.
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.

The School of Medicine’s researchers have traced the connection to a defective immune cell’s sweet tooth.

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 attack risk 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 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 over 80 have had shingles, Weyand noted, and “old have had and 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 lies dormant inside our nerve ganglia. In older or immune-compromised people, the long-dormant virus can re-activate, 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 cells' innate immune system, informed the researchers, becomes hijacked 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 analyzing data management and assessment, information processing and software and technology-infrastructure development could help. A vital component of this approach is to take advantage of the benefits of big data. This will require changes to the health care provider’s education and the skills to deliver successful patient outcomes.

Similarly, the rise in wearable devices, genome sequencing and other technologies gives patients more information than ever about their own health, making great strides in patient health. Providing patients with necessary information can make them better informed decisions.

“An opportunity and a challenge”

“Today, health care is becoming 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 equip 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 large scale use of 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 the 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 risks across the U.S. health care system threaten to undermine the big role big data can play.

• Reforms to electronic health record 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/health-trends. Print copies of the report are requested at 850-1265.
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 ever had an ophthalmologist check your eye, or your heart was imaged by MRI, you’ve probably had OCT done. OCT is a medical imaging technique that uses light to create high-resolution, cross-sectional images of tissues. It is commonly used in the diagnosis and monitoring of ocular diseases, such as macular degeneration, diabetic retinopathy, and glaucoma, and also in the assessment of tissue damage in other parts of the body, such as the heart and arteries.

The technique works by shining a laser light into the tissue and analyzing the light that is reflected back. Because different tissues have different optical properties, the reflected light is scattered differently, allowing OCT to image structures at different depths. OCT images are often used to diagnose and monitor diseases such as diabetic retinopathy, macular degeneration, and glaucoma.

However, despite its widespread use, OCT has limitations. One of the main challenges is the lack of high-resolution imaging in three dimensions (3D). This is because OCT images are typically captured as a series of 2D cross-sectional images, which can make it difficult to visualize the full 3D structure of a tissue.

But now, a team of researchers from Stanford University has developed a new method to improve OCT imaging. They have combined the technique with a new imaging modality called nanophotonics, which allows for high-resolution imaging in 3D.

The researchers achieved this by integrating a high-fidelity, low-cost chamber into the OCT system. The chamber contains a pair of lenses, which are used to record the light that is reflected back from the tissue. This creates a holographic image of the tissue, which can then be reconstructed to generate a 3D image.

The new technique can achieve a resolution of around 40 micrometers, which is comparable to the resolution of confocal microscopy, a widely used technique for imaging 3D structures. The researchers argue that this is a significant improvement over traditional OCT imaging, which typically has a resolution of around 10 micrometers.

The technique could have a wide range of applications, from medical imaging to materials science. In medicine, it could be used to improve the diagnosis and treatment of eye diseases, or to monitor the progression of diseases such as diabetic retinopathy or macular degeneration.

In addition, the researchers are also working on developing a compact OCT system that could be used in doctors’ offices or other settings, making high-resolution imaging more accessible to a wider range of patients.

The researchers are also exploring ways to improve the sensitivity and specificity of the technique, and are working on developing new applications for it. For example, they are exploring the use of OCT for imaging the heart, where it could be used to monitor the progression of heart disease.

Overall, the new technique represents a significant advance in OCT imaging, and could pave the way for new applications and improvements in the field.
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.

Nelsen, who came to Stanford from Stanford to the University of Chicago, became a member of Stanford’s world-renowned Hodgkin’s lymphoma program’s radiation therapy team as an early pioneer in the treatment of cancer in its infancy. He conducted diagnostic surgical procedures during clinical trials that helped radiologists 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 where I saw patients when I was at Stanford,” said Ashley. “I’m glad to be here.”

Nelsen graduated early from Stanford 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 Stanford.

“Nelsen was a member of the Institute for Electrical and Electronics Engineers, as well as several surgical societies,” said Rosenberg, professor emeritus of oncology.

“Goal, simply stated, is to enable the Stanford community to do cool stuff to improve health care with technology,” said Mintra Tazikha, 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 important community, providing infrastructure and support in the field of digital health.

“We facilitate a 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 mindsets in health technology — Alia Crum, PhD, assistant professor of psychopathology.

• Re:Claim: A virtual therapist for stroke patients — Matthew Wheeler, MD, PhD, clinical assistant professor of medicine and of neuroscience.

• Stop, watch: Reducing hyperactivity and attention-focusing problems among adults — Lorene Nelson, PhD, assistant professor of psychiatry and behavioral sciences.

• 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.

“We aim to facilitate the advance of the field of digital health by enabling research collaboration between faculty members and technology companies,” said Rosenberg, professor emeritus of oncology.

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Graduation
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AUSTIN 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.

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.”

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 two Pompei, MD, clinical professor of medicine, received the Arthurr L. Bloomfield Award in Recognition of Excellence in the Teaching of Clinical Medicine.
Erika Schillingier, MD, clinical professor of medicine, received the Franklin G. Ebaugh, Jr. Award for Excellence in Advising Medical Students.
James Lai, MD, clinical associate professor of surgery, received the Alvin 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 patients.

Sakthi Srivatsava, MD, associate professor of surgery, director of Digital MEdicine and chief of clinical neuroimmunology, and two

A 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 our Connected, visit http://med.stanford.edu/connected.html
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 generate 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, each message, or 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 2015, members of Barna’s lab showed that one core ribosomal protein called RPL36L1 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 Fuji 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 in terms of the exact stoichiometry of these proteins, there are significant differences among individual ribosomes,” said Barna. “But what does this mean when it comes to thinking about fundamental aspects of a cell, how it decides on cell fate?”

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 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 gene regulation within the cell, they play no role in the regulation of genetic expression as is, in retrospect, a bit silly.”

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

The study was supported by the National Institutes of Health and the National Academy of Sciences. Kyle Kovary and Sloane Grodner; research assistant Colin Holbrook; research assistant Donna Yu; postdoctoral scholar Remy Nowak; and crafting their own discoveries. They are the future of medicine, and we’re excited about that.”

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 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. The lead author holds the Donald E. and Debra J. Blau Chair in Stem Cell Biology and of Genetics also supported the work.

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 tissue. But it’s not entirely clear what signals present in inflammation activate the stem cells.

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

Ho and Pallad 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 dramatically increased within a three-day period after injury, indicating it is a transient, naturally occurring immune mediator.

To determine the mechanism of action, Ho and Palla created a genetically modified 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 PGE2. The researchers caused by injection of a toxin or by application of cold temperatures. (The mice were not sacrificed for the purpose of this study, 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 six- to 10-fold compared to 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, they showed a transient but significant increase in unaffected muscle regeneration and even increased strength,” said Palla. “Conversely, if we inhibited the ability of the muscle stem cells to produce PGE2 by blocking the expression of EP4 or by giving them a single dose of a drug that suppresses 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 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. They have identified whether and how aging affects the stem cells’ response.

Stanford authors are former technician Matthew Blane; graduate student Nora Yucel; postdoctoral Xu Xin Wang, PhD; former graduate student Remy Nowak; and postdoctoral scholars are Colin Holbrook; research assistant and lab manager Peggy Kraft; and Scott Douglis, PhD, professor 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.
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 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 infirmity and a lack of engagement with patients. Moreover, his studies have found that 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, he said, that is “eroding the soul of medicine.”

“I think most health care leaders now realize this is critical to their organization’s mission,” Shanafelt said. “They say, ‘We get it, and we want 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.”

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. Among the absolute burnout rates among Mayo physicians declined 7 percent over two years, despite an 11 percent rise in the rate among physicians nationally, according to surveys showed. A more recent assessment found the burnout rate among Mayo physicians was about two-thirds that of physicians nationally.

Shanafelt’s 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, as well as training and ways to cultivate compassion and resilience, as well as a literature and a dinner series in which physicians explore the challenges and successes of individual doctors. The center also aims to relieve some of the burden on physicians by improving efficiency of medical 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, called the WellMD center “grounded closely with Shanafelt over the past year on projects of mutual interest.”

“All of us have had the privilege 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 COE of Packard Children’s Hospital at Stanford, said Shanafelt’s appointment as the leader of Stanford Medicine’s wellness effort, in addition to his work in physician well-being, is an international expert in the treatment of chronic lymphocytic leukemia. He said he plans to continue to work with all of Shanafelt’s past work and to commit 30 percent of his time to clinical research and the care of patients with the disease.

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.

Anusman 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.

The awards are designed to help support the next generation of scientists in cancer immunotherapy by supporting promising young researchers doing innovative work that has the potential for great impact. The Parker Institute’s investigators were one of 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 toward 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 subjects for a longer period of time to prevent cancer from recurring.

Satpathy has been working in the lab of Bohman, MD, a 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 a new genome-sequencing methods to study how T cells funnel undirected change in the presence of cancer.

In so doing, “We can see what is happening in patients that is working or isn’t, what is not, and incorporate those insights into our design to better therapeutics,” Satpathy said. Now a third-year resident in pathology, he will continue to work in Chang’s lab while he transitions to being an oncology investigator and faculty member.

“Tait Shanafelt is one of the people that is working hard on this issue and what is not, and incorporating those insights into our design to better therapeutics,” Satpathy said. Now a third-year resident in pathology, he will continue to work in Chang’s lab while he transitions to being an oncology investigator and faculty member.

“I think that transition is particularly difficult both in clinical practice and developing relationships with other scientists and collaborators,” he said. “This award supports it both in clinical practice and developing relationships with other scientists and collaborators,” he said. “This award supports it both in clinical practice and developing relationships with other scientists and collaborators.”