Source of opioids’ side effects identified
By Tracie White

A commercially available drug may help drastically reduce two side effects of opioid painkillers — a growing tolerance to them and a paradoxical increased sensitivity to pain — without affecting the drugs’ ability to reduce pain, according to a study by researchers at the School of Medicine.

These two side effects often mean patients require higher doses of opioids to maintain pain relief, increasing the risk of addiction and respiratory failure. Opioid overdoses were responsible for more than 20,000 deaths nationwide in 2015, according to the American Society of Addiction Medicine, and are now the leading cause of accidental death in the United States.

“In some patients, you don’t have much margin between how much painkiller you can give and their ability to breathe normally, or the occurrence of other significant side effects,” said Gregory Scherrer, PhD, PharmD, assistant professor of anesthesiology, perioperative and pain medicine and of neurosurgery. “Our goal was to understand how opioids cause their side effects, to find ways to separate these detrimental side effects from pain relief properties and to make these painkillers safer.”

Scherrer is the senior author of the study, which was published online Jan. 16 in Nature Medicine. The lead authors are postdoctoral scholars Gregory Corder, PhD, and Dong Wang, PhD; anesthesiology instructor Vivialle Taw-fik, MD, PhD; and graduate student Elizabeth Sypek.

Working in mouse models, Scherrer and his colleagues found that tolerance and increased sensitivity to pain may be specifically caused by opioids’ effect on peripheral pain neurons in the body, not those in the spinal cord and brain. They also established that contrary to the prevailing view in the field, microglia — non-neuronal cells found in the spinal cord and brain — are not initiating opioid’s side effects because they lack the gene that forms the receptors necessary to cause them.

By using a drug that blocks only the effects of opioids on the periphery, they were able to eliminate the two side effects without reducing pain relief.

“We demonstrate that these two side effects can be drastically reduced with the use of an already used compound, methylnaltrexone bromide, currently used to combat constipation, which is another unwanted side effect of opioids, while still maintaining pain relief,” Scherrer said.

Methylnaltrexone bromide is approved by the Food and Drug Administration for the treatment of opioid-induced constipation.

Clinical trials needed
Clinical trials are now needed to test whether the findings hold true in humans, with the goal of reducing the number of deaths from overdoses while improving the function of prescription opioid painkillers, Scherrer said.

Growing concern about an epidemic of opioid-painkiller abuse has drawn the attention of physicians, patients and public health authorities. According to the Centers for Disease Control and Prevention, about 100 Americans die each day from drug overdoses, and more than half of those deaths involve opioid pain relievers.

From a clinical standpoint, these pain relievers not only present safety risks, but they often prove a disappointment in how well they work to control pain, said co-author David Clark, MD, PhD, a Stanford professor of anesthesiology, perioperative and pain medicine who treats patients at the Palo Alto Veterans Affairs Health Care System.

“They don’t in general provide substantial pain relief for a long period of time,” said Clark. “The prevalence of chronic pain in veterans is unusually high, he said. In addition to the chronic pain from such illnesses as cancer and diabetes, many veterans also face lifelong pain from battle wounds, such as traumatic brain injuries, shrapnel injuries and injuries to limbs.

“Once patients start on opioids, the drugs may work for weeks or months, but then it’s common to see the pain relief dissipate, and these patients face the decision of whether or not to increase the dose,” Clark said. "With increasing doses comes the increasing risk of adverse events.”

See OPIOIDS, page 7

Gay health workers face tough choices where homosexuality is a crime
By Ruthann Richter

Jason Nagata, MD, sat in a wooden pew in a Seventh Day Adventist church in Kenya, listening to the pastor thunder away about the “abomination” of homosexuality. Nagata, then a medical student, began to sweat profusely, his face dripping with tears. Flank ing him in the church pew were members of his Kenyan host family, who had no idea he was gay.

“It was clear all the people in the church had similar viewpoints, as they were nodding in agreement with the pastor,” he said. “I think I was just trying as hard as I could not to let anything show on my face.”

In a recently published commentary, Nagata writes about the challenges of being gay and doing global health work in countries where homosexuality is a crime, punishable by death or imprisonment, and where those legal constraints are often mirrored in societal attitudes. The commentary, written while he was a pediatric resident, was published online Jan. 16 in Nature Medicine, implicates this inflammatory process as a driver of cardiovascular disease and increased rates of mortality overall. Metabolites, or breakdown products, of nucleic acids — the molecules that serve as building blocks for our genes — circulating in the blood can trigger this inflammatory process, the study found.

Caffeine may counter systemic inflammation
By Bruce Goldman

School of Medicine scientists have unearthed a connection between advancing age, systemic inflammation, cardiovascular disease and caffeine consumption.

Extensive analysis of blood samples, survey data and medical and family histories obtained from more than 100 human participants in a multiyear study has revealed a fundamental inflammatory mechanism associated with human aging and the chronic diseases that come with it.

The study, which was published online Jan. 16 in Nature Medicine, implicates this inflammatory process as a driver of cardiovascular disease and increased rates of mortality overall. Metabolites, or breakdown products, of nucleic acids — the molecules that serve as building blocks for our genes — circulating in the blood can trigger this inflammatory process, the study found.

The study also provides evidence that caffeine and its own metabolites may counter the action of these circulating nucleic-acid metabolites, possibly explaining why coffee drinkers tend to live longer than abstainers.

Co-administration of all noncommunicable diseases of aging are associated with chronic inflammation,” said the study’s lead author, David Furman, PhD, a consulting associate professor at the Stanford Institute for Immunity, Transplantation and Infection. More than 1,000 papers have provided evidence that chronic inflammation contributes to many cancers, Alzheimer’s disease and other dementias, cardiovascular disease, osteoarthritis and even depression, he said.

“It’s also well known that caffeine intake is associated with longevity,” Furman said. “Many studies have shown this association, we’ve found a possible reason for this may be so.”

Mark Davis, PhD, a professor of microbiology and immunology and the director of the Stanford Institute for Immunity, Transplantation and Infection, shares senior authorship of the study with Benjamin Faustin, PhD, a cell biologist at the University of Bordeaux in France. Davis is the senior author of the study, which was published online Jan. 16 in Nature Medicine. The lead authors are postdoctoral scholars Gregory Corder, PhD, and Dong Wang, PhD; anesthesiology instructor Vivialle Taw-fik, MD, PhD; and graduate student Elizabeth Sypek.

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See OPIOIDS, page 7
Diabetes impairs activity of bone stem cell, inhibiting fracture repair

By Krista Conger

Bone fractures in diabetic mice heal better than in the bones of mice with diabetes, which stimulates the activity of skeletal stem cells, according to a study by researchers at the School of Medicine.

The protein counters a decrease in stem cell activity that the researchers believe is caused by a decrease in the number of healthy mouse models of diabetes and in bone samples from diabetic patients who had undergone joint replacement surgery. The researchers hope the discovery will lead to ways to help people with diabetes heal more efficiently from broken bones.

“We’ve uncovered the reason why some patients with diabetes don’t heal well from fractures, and we’ve come up with a solution that can be locally applied during surgery to repair the break,” said Michael Longaker, MD, co-director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine. “Diabetes is rampant worldwide, and any improvement in the ability of affected people to heal from fractures will be crucial for this large population of people with diabetes who have severe impairments of the skeletal system, including bone, and are at risk of developing diabetes-related fractures. A greater understanding of the mechanisms that underlie the impaired healing of bone in diabetes will improve our ability to develop new treatments for bone fractures in people with diabetes.”

The study was published Jan. 11 in Science, Longaker said. The researchers found that a protein known to play a critical role in many biological processes, including inflammation, metabolism and development of biological structures, identified and described a population of cells in the bones of mice that serve as a niche. When T evlin and her colleagues analyzed that environment, they found that the diabetic mice responded differently than wild-type mice, the researchers reported that diabetic mice heal more efficiently from broken bones.

Diabetes mellitus is a metabolic disease characterized by the inability to either produce or respond appropriately to insulin. It affects hundreds of millions of people worldwide and is increasing in prevalence. In addition to causing dangerous swings in blood sugar levels after meals, the condition leads to many other debilitating symptoms, including an impaired ability to heal soft tissue injuries and fractures. The precise molecular reason behind this impaired bone healing has been unknown, however.

Longaker, Chan and Tevlin built on previous research in which they and colleagues showed that an abnormal inflammatory response in the bone marrow environment might be interfering with fracture healing in diabetes. They found that the diabetic mice were less likely to heal their fractures compared to the control mice, and that the diabetic mice had significantly lower levels of cells than did the control animals.

Signaling problem
A series of experiments ruled out a systemic reason for this reduction in cell numbers, and also confirmed that the cells themselves were fully functional. That left only a potential problem with the signals that the cells were receiving from the surrounding environment, or niche. When Tevlin and her colleagues analyzed that environment, they found that the diabetic animals produced significantly lower levels of a family of signaling proteins, called hedgehog, that is known to play a critical role in many biological processes, including embryonic development and tissue regeneration.

“Next we had to test whether adding the hedgehog signaling pathway could improve bone healing in nondiabetic mice. They found that control mice exposed to a molecule that blocked the pathway regrew bone that was weaker and more brittle — just like the diabetic animals. “This effect may be even bigger in patients who are type 2 diabetic,” said Longaker.

The researchers collaborated with co-author Philip Beachy, PhD, professor of biochemistry and of developmental biology, to test whether artificially blocking the hedgehog signaling pathway could improve bone healing in nondiabetic mice. They found that control mice exposed to a molecule that blocked the pathway regrew bone that was weaker and more brittle — just like the diabetic animals.
Bones continued from page 2

and postdoctoral scholar Xinning Tong, PhD, said the team found that replacing hydrogel into which the hedgehog sig-

naling proteins were embedded. The gel was then placed into diabetic mice. "And these animals healed just like normal mice," said Longaker, who holds the

PhD, professor of neurobiology, of developmental bi-

ology and of neurology and neuroscientific studies. "An abnormally high level of them turns up in susceptible

disease in all the wrong places in brain-tissue samples

from patients with brain injuries and major neurologi-

cal disorders such as Parkinson's to multiple skel-

ter sclerosis. The implications for treating these diseases are profound."

Barres, who has spent three decades focusing on

brain cells that aren't nerve cells, called the findings "the most important discovery my lab has ever made." Stan-

ford postdoctoral scholar Shane Liddelow, PhD, is the study's lead author.

Up to now, the pharmaceutical industry has mostly targeted nerve cells, also known as neurons, Barres said. But a broad range of non-neuron brain cells are targets, by blocking astrocytes' metamorphosis into toxic cells, or by pharmacologically countering the neuron-killing toxicity those harmful cells almost certainly secrete.

Role of astrocytes

Once thought of as mere packing peanuts whose job it was to clear out debris from juggling when we jog, astrocytes are now understood to provide critical hands-on support and guidance to neurons, enhancing their sur-

gvival and growth, health and survival near the stroke site.

In 2012, Barres and his colleagues resolved that am-

teinase A1s, which are a component found in the cell walls of bacteria, they observed that resting astrocytes some-

how wind up getting transformed into A1s, which are primed to produce large volumes of pro-inflammatory substances. A1s, on the other hand, are induced by oxygen deprivation in the brain, which occurs during stroke. Resting astrocytes support nerve cell growth, health and survival near the stroke site.

"This raised two questions: How are A1s generated? And once they're generated, what do they do? The new study answers both questions.

Pro-inflammatory factors

In addressing the first question, the study showed that the brain's immune cells, microglia, which become activated by LPS exposure as well as in most brain inju-

ries and diseases, begin spewing our pro-inflammatory factors that change astrocytes' behavior.

In a series of experiments using laboratory mice, the scientists identified three pro-inflammatory factors whose production was ramped up after LPS exposure: the inflammatory cytokines TNF-alpha, IL-1 alpha, and IL-6. 95% of these substances are secreted exclusively by microglia. Each, by itself, had a partial A1-inducing effect on rest-

ing astrocytes. Combined, they propelled resting astro-

cytes into a full-fledged A1 state.

Next, the researchers confirmed that A1s activates reactive migraine synapses, which Barre's group has shown are essential to the for-

mation and functioning of synapses, and instead be-

came toxic to neurons.

In vertebrates, nerve cells called retinal ganglion cells send information from the retina to vision-processing centers in the brain. RGCs can in thrive in culture, but only if accompanied by astrocytes. The scientists cul-
tured rodent RGCs with either resting or A1 astrocytes and counted the resulting synapse numbers. RGCs cul-
tured with A1 astrocytes formed synapses only up to 15% as many as synapses as RGCs grown with resting astro-

cytes, and those that formed didn't work very well.

Further experiments showed that A1s lose rest-

ing astrocytes' capacity to prune synapses that are no longer needed or no longer functional whose continued existence undermines efficient brain function.

Indeed, when the researchers cultured healthy

RGCs with increasingly stronger concentrations of the bath in which A1s had been bathing, almost all the RGCs eventually died. This and other experi-

ments showed that A1s secrete a powerful, neuron-

killing toxin.

The same treatment killed many other types of neurons, including both the spinal motor neurons that die in amyotrophic lateral sclerosis and the hu-

man dopaminergic neurons whose mysterious loss is at the core of Parkinson's disease. A1 bathwater also impaired the development of yet another class of neurons, the dopaminergic neurons of the nigrostriatal dopaminergic pathway in mice. The finding, published in Nature, is "the most important discovery my lab has ever made," said the study's senior author, Ben Barres, MD, PhD, professor of neurobiology, of developmental bi-

ology and of neurology and neurological sciences. "An

continued from page 2

in this case it held important clues.

"What we saw in these human sam-

ples completely echoed what we saw in the mouse samples. In the diabetic patients displayed signifi-

antly reduced expression of these im-

portant signaling molecules," Longaker, Chan and T evlin believe the inhibition of the hedgehog signaling pathway arises from diabetes-associated inflammation. This inflammation activates a molecule called tumor necrosis factor alpha. TNF-alpha levels are known to be elevated in many diseases, including diabetes. The researchers observed a correspond-

ing increase in their mouse models of diabetes and diabetes. As the levels of TNF-alpha inhibited the expression of some hedgehog family members, decreased expression of hedgehog activity, however, could have other dire consequences for an animal or a hu-

man patient because TNF-alpha plays many important biological roles.

"Here we've devised a feasible strategy for reversing a tissue-specific pathology — the inability to heal skeletal fractures — in a complex metabolic disease like diabetes, through the local application of a compound to stimu-

late the activity of adult stem cells," said Longaker. "We anticipate that hedgehog-mediated molecular therapies that directly target stem cells in human patients could be therapeutic."

More research is necessary before try-

ing this approach in humans, but the音箱 with diabetes and the data on the inhibition of hedgehog protein will be shown to be both safe and effective. The find-

ings also show that A1s. The researchers believe that specific stem cells are likely to play vital roles in tissue regeneration and response to injury.

"This research represents a significant step toward realizing the prom-

ise of Proposition 71, which established the California Institute for Regenerative Medicine," said Chan. "We've looked to stem cells to learn why people with dia-

betes don't heal bone fractures properly, and come up with an approach that we are excited to try in the clinic."

The paper provides a complete list of the Stanford co-authors of the study. The research was supported by the National Institutes of Health, the Christopher and Dana Reeve Foundation, the Novartis Institute for Biomedical Research, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, the JPB Foundation, the Cure Alzheimer's Fund, the Glenn Foundation and Vincent and Stella Coates.

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naling proteins were embedded. The gel was then placed into diabetic mice. "And these animals healed just like normal mice," said Longaker, who holds the

PhD, professor of orthopedic surgery, to obtain bone samples from patients with osteoarthritis who were undergoing joint replacement for osteoarthritis. They compared the expression of hedgehog signaling pathway by these samples with others obtained from non-

diabetic patients. Normally this pathway would be discarded by the surgeon, but

regenerative disorders

While most of us haven't heard of astrocytes, these cells are four times as plentiful in the human brain as nerve cells. Now, a team led by researchers at the School of Medicine has found that astrocytes, which perform many indispensable functions in the brain, can take on a villainous character, destroying nerve cells and likely driving many neurodegenerative disorders.

A study describing the findings was published online Jan. 18 in Nature.

"We've learned astrocytes aren't always the good guys," said study senior author, Ben Barres, PhD, professor of neurobiology, of developmental bi-

ology and of neurology and neuroscientific studies. "An aberrant function of them turns up in susceptibility

The scientists then turned their attention to the astrocytes that are in the prefrontal cortex, a region of the brain where the disease was most active. For example, in the samples from Alzheimer's patients, nearly 60 percent of the astrocytes present in the frontal cortex, a region where the disease takes a great toll, were of the A1 va-

riety. Because A1s are highly toxic to both neurons and oligodendrocytes, these findings strongly imply that A1 formation is helping to drive neurodegeneration in these disorders.

An effort to identify the neurotoxin secreted by A1 astrocytes is underway, Barres said. "We're very excited by the idea of identifying the healthy and precisely diag-

nose and treat disease in the brain.

Barres is the co-founder of a biotechnology com-

pany, Neuronet Therapeutics, which has been filed for a patent, an inhibitory antibody to C1q. Drugs to block TNF-alpha and IL-1 alpha already exist.

Other Stanford co-authors are graduate student Kevin Guettemplan; postdoctoral scholars Laura Clarke, PhD, Todd Peterson, PhD, Brooke Napier, PhD, and Christopher Bohlen PhD; Frederick Bennett, MD, an instructor of psychiatry and behavioral sciences; medical student Markio Bennett, PhD; life science research assistant Alexandra Munch; former postdoctoral scholars Won-Suk Chung, PhD; and Marion Buckwalter, MD, PhD, associate professor of neurosurgery and of neurol-

ogy and neurological sciences. Researchers from the University of California-San Francisco, the Technical University of Munich, Bos-

ton Children's Hospital, Johns Hopkins University and Harvard University also co-authored the work.

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Stanford’s Department of Neurobiology also sup-

ported the work.

"The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and treat disease by understanding the healthy and precisely diag-

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ported the work.
A new technique allows researchers to see where immunity cells go as they hunt down tumors in the human body. The imaging technique also reveals whether the immunity cells, called T cells, have found a tumor; how many T cells have arrived at the tumor; and whether the T cells are alive.

The ability to see whether T cells are attacking tumors is useful both for clinicians trying to learn if a treatment is working in an individual cancer patient and also for researchers trying to understand how immunity therapies currently work.

A paper describing the work was published online Jan. 18 in Science Transla- tional Medicine. The senior author is Sanjiv “Sam” Gambhir, MD, PhD, professor and chair of radiology at Stanford. Lead authorship of the study is shared by former Stanford postdoctoral scholars Khun Khu, MD; Timothy Witney, PhD; and Shahriar Vaghjii, PhD.

“One can now watch anywhere in your body where those T cells may be,” said Gambhir, who holds the Virginia and D.K. Ludwig Professorship in Cancer Research. “This is the first demonstration in humans of actually noninvasively watching cancer patients’ immune system reactions with reporter gene technology. It’s never been done before in a living human, and without the need to remove any tissue.

The work was done in patients with a type of deadly brain cancer called glioblastoma, but the groundbreaking technique could be used to track immunity cells fighting any kind of cancer, Gambhir said.

The limitations of immunotherapy

In one form of standard immunother-apy, a medical team harvests T cells from a cancer patient’s blood and geneti- cally engineers them to do a better job of hunting down and killing the patient’s cancer cells. Such immunotherapy some- times works, but not always.

By Jennie Dusheck

Wearable sensors can tell when you are getting sick, study shows

By Jennie Dusheck

Wearable sensors that monitor heart rate, activity, skin temperature and other variables can reveal a lot about what is going on inside a person, including the onset of disease from infection or even insulin resis- tance, according to a study by researchers at the School of Medicine. An important component of the ongoing study is to establish a range of normal, or baseline, values for each person in the study and when they are ill. “We want to study people at an individual level,” said Michael Snyder, PhD, professor and chair of genetics.

Snyder is the senior author of the study, which was published online Jan. 12 in PLOS Biology. Postdoctoral scholars Alice L. Duan, PhD, and Jennifer Duan, PhD, and software engineer Denis Salinas share lead authorship.

Altogether, the team collected nearly 2 billion measurements from each participant’s wearable biosensor devices and period data from laboratory tests of their blood chem- istry, gene expression and other measures. Participants wore between one and seven commercially available activity monitors and other monitors that collected more than 250,000 measurements a day. The team collected data on weight; heart rate; oxygen in the blood; skin temperature; activity, including sleep, steps, walking, biking and running; calories expended; acceler- ation; and even exposure to gamma rays and X-rays.

“I was very impressed with all the data that was collected,” said Eric Topol, MD, professor of genomics at the Scripps Research Institute, who was not involved in the study. “There’s a lot here of a lot of sensors and a lot of different data on each person.”

The study demonstrated that, given a baseline range of values for each person, it is possible to monitor deviations from normal and associate those deviations with environmental conditions, illness or other factors that affect health. Distinc- tive patterns of deviation from normal seem to correlate with particular health problems. Algo- rithms designed to pick up on these patterns of change could potentially contribute to clinical diagnostics and research.

The work is an example of Stanford Medi- cine’s focus on precision health, whose goal is to anticipate and prevent disease in the healthy and to precisely diagnose and treat disease in the ill.

An unexpected diagnosis

On a long flight to Norway for a family vaca- tion last year, Snyder noticed changes in his heart rate and blood oxygen levels. As one of the 60 participants in the digital health study, he was wearing seven biosensors. From previous trips, Snyder knew that his oxygen levels normally dropped during air flights and that his heart rate increased at the beginning of a flight — as occurred in other participants. But the values typically returned to normal over the course of a long flight and after landing. This time, his num- bers didn’t return to baseline. Something was up, and Snyder wasn’t completely surprised when he went on to develop a fever and other signs of illness.

Two weeks earlier, he’d been helping his brother build a fence in rural Massachusetts, so his biggest con- cern was that he might have been bitten by a tick and infected with Lyme disease. In Norway, Snyder per- suaded a doctor to give him a prescription for doxy- cine, an antibiotic known to combat Lyme disease.

Subsequent tests confirmed that Snyder had indeed been infected with the Lyme microorganism. Snyder was impressed that the wearable biosensors picked up the infection before he even knew he was sick. “Wearables helped make the initial diagnosis,” he said. Subsequent data analysis confirmed his suspicion that the deviations from normal heart rate and oxygen levels on the flight to Norway had indeed been quite abnormal.

“The fact that you can pick up infections by moni- toring before they happen is very provocative,” said Topol.

More discoveries

For Snyder, the Lyme diagnosis is just the tip of the iceberg — part of very early work to begin querying massive data sets of health information. The results of the current study raise the possibility of identifying in- fectious diseases or other conditions in individuals who may not even know they are getting sick. For example, in several par- ticipants, higher-than-normal readings for heart rate and skin temperature correlated with increased levels of C-reactive protein in blood tests. C-reactive protein is an immune system marker for inflammation and often indicative of infection, autoimmune diseases, develop- ing cardiovascular disease or even cancer. Snyder’s own data revealed four separate bouts of illness and inflam-

The future of wearable devices

During a visit to a doctor, patients normally have their blood pressure and body temperature measured, but such data is typically collected only every year or two and often ignored unless the results are outside of normal range for entire populations. But biomedical researchers envis- age a future in which human health is monitored continuously.

“We have more sensors on our cars than we have on human beings,” said Snyder. “As the future, he said, he expects the situation will be re- versed and people will have more sensors than cars do. Already, consumers have purchased mil- lions of wearable devices, including more than 50 million smart watches and 20 million other fitness monitors. Most monitors are used to track activity, but they could easily be adjusted to more directly track health measures, Snyder said.

With a precision health approach, every per- son could know his or her normal baseline for dozens of measures. Automatic data analysis could spot patterns of outlier data points and flag the onset of all health, providing an opportunity for intervention, prevention or cure.

Other Stanford-affiliated co-authors of the study are researcher Gao Zhe; postdoctoral scholar Wenyu Zhou, PhD, and Sajeev Weerasinghe-Florenza Rose, MD, PhD; research di- etician Dalia Perlman; undergraduate summer interns Ryan Runge and Somalee Schüssler-Fiorenza Rose, MD, PhD; research di- etician Shannon Rego; high school student Ria Sonecha; Somalee Datta, PhD, director of the Genetics Bioinfor- matics Service Center; and Tracey McLoughlin, MD, associate professor of medicine.

Researcher Elizabeth Collbert, of the Vet- erans Affairs Palo Alto Health Care System, is also a co-author.

This research was funded by the National Institutes of Health, the National Institute of Diabetes and Di- gestion and Kidney Diseases and a gift from Bert and Candace Forbes.

Stanford’s Department of Genetics also supported the work. See IMMUNOTHERAPY, page 5
Digital health center aims to connect faculty with technology companies

By Tracie White

The School of Medicine has launched a center to support collaborations between Stanford faculty and Silicon Valley technology companies to develop, test and implement new digital health tools.

The Center for Digital Health aims to advance the field of digital health by promoting these partnerships, performing early research and educating the next generation of physicians and digital health care leaders.

“Digital health is a space where Stanford should be leading the way,” said Sumbul Desai, MD, clinical associate professor of medicine and executive director of the center. “The new center will be focused on leveraging our resources and encouraging collaborations that will lead to breakthroughs through digital technology.”

Lloyd Minor, MD, dean of the School of Medicine, said the center will further advance Stanford’s mission to improve healthcare through precision health. “With the addition of our biomedical expertise and location in Silicon Valley, Stanford Medicine is uniquely positioned to be a leader in the field of digital health,” Minor said.

The new Center for Digital Health fits well within the framework of the biomedical revolution in precision health at Stanford by using the most advanced digital technologies and tools to develop care that is tailored to individual patients.

Connecting and enabling faculty

“The goal of the center is to encourage collaborations that will help create the next generation of health care information technologies,” said Laura Cheung, MD, MBA, clinical assistant professor of medicine and senior director of strategy and operations for the center.

The center grew out of a need to provide support and guidance to faculty who were repeatedly being contacted by both startups and established technology companies with offers to collaborate, Desai said.

“We wanted to leverage that interest and generate more opportunities for the faculty by providing the infrastructure and resources needed to encourage these relationships,” Desai said. “We can help connect interested faculty with industry, or vice versa. Say, for example, there’s a faculty member interested in pulmonary digital health research. We may be able to connect that faculty member with the same interest. We can help connect them.”

Doing research quickly, inexpensively

“There are hundreds upon hundreds of digital health start-ups now, and it is very difficult for patients, doctors, hospital insurers, regulators and investors to know which solutions will work and which will stick,” said Minutu Turakhia, MD, assistant professor of cardiovascular medicine and senior director of research and innovation at the center. “High-quality evidence is needed to make informed decisions. We generate this evidence quickly and cheaply, targeting the real-world outcomes that matter for all of these stakeholders.”

Turakhia leads efforts to advance research in digital health at Stanford that ranges from technology assessment and implementation studies to multicenter trials. He is the principal investigator for five digital health trials. The largest of these is a 25-site, 400-patient ran-domized trial to explore digital interventions combined with health coaches to determine whether they improve medication adherence for people with atrial fibrillation, which affects 4 million U.S. adults.

Even after generating rigorous evidence, there can be a long, complicated path to implementation with many unanswered questions, Turakhia said. Such questions include: What is the best way to incorporate new digital tools into the practice of health care? Will new advances actually improve patient care? Are they worth the costs?

“Currently there is very little evidence to support how best to incorporate digital tools into practice,” Cheung said. “Stanford faculty have the expertise to help with the design and implementation of new digital health tools.”

Training and education

The center will provide training to physicians in digital health medicine at Stanford through fellowships, internship opportunities, conferences and traditional classroom material, Desai said. In addition, the center will offer educational programs to industry members.

The center is also accepting proposals for health care research projects focused on innovative uses for Apple Watches. In addition to up to 1,000 of the watches, the center will award $10,000 to the winning project for one year, starting in April.

Learn more about the center at http://med.stanford.edu/cdh.html.

Lauren Cheung
Sumbul Desai
Minutu Turakhia

Immunotherapy

continued from page 4

times works, but most often does not. But it’s hard for clinicians to tell when it’s not working, and challenging to know why it’s not.

“Part of it is chance and part of it is a problem,” said Gambhir. “How do you know whether the T cells are doing their job or not? There’s no way to tell.”

Right now, the only way to tell if T cells are attacking the cancer is to wait to see if the tumors shrink, which can take months. And whereas when treatment is working, some tumors may appear to get bigger for a while — a result of inflammation. So it can be tricky to tell if a cancer that doesn’t necessarily mean treatment has failed. Even if clinicians are sure treatment has failed, they don’t know why. Did the T cells not reach the tumor? Or did the T cells get to the tumor but fail in their attack?

“We are shooting blind,” said Gambhir. “We don’t know if the T cells are actually attached to tumor cells. But if the T cells attack the cancer cell — and whether the cells’ locations tell researchers to see immunotherapies in action and thus be better able to understand, and hopefully fix, things that go wrong with them.”

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 diagnosing the dogs’ human handlers where both the bloodbonds and the prey are. In the same way, the researchers could tell when T cells were near their prey — a tumor — because they could see the protein products of the reporter genes clustering there.

PET scans showing the T cells’ locations tell researchers how many T cells have reached a tumor — whether it’s 6 million cells or 50 million — and whether the cells are there. “And you can come back and redo the imaging after a few days, weeks, or months,” said Gambhir. “The new technique can do things that PET scans can’t.”

One thing the new technique cannot do is determine whether the T cells are actually attached to tumor cells. But that’s coming, Gambhir said.

“Right now, the reporter gene is always on,” he said. “But we could change the reporter gene so it only comes on after it latches onto the tumor cell and kills it.” That approach works in mice, but isn’t quite ready for human trials, he said.

Surprises

The new T cell imaging technology can also reveal, indirectly, where other unsuspected tumors are. “In one patient,” said Gambhir, “the T cells went to the tumor in the brain, as expected. But some of the T cells wandered away to another area of the brain.” Even though the second tumor had been invisible to standard imaging, the “bright” T cells in the PET scan revealed its presence.

“The biggest surprise, said Gambhir, is that the technique worked at all. Some people are saying, ‘Is this possible? How did they get this to work?’”

Part of it is chance and part of it is a lot of his team’s prior research efforts, he said, estimating that his lab has produced over 15 years of work with the quest to make the T cell imaging technology work, first in animals, and, now, in humans.

Glioblastoma is a particularly intrac-
Bodywide immune response important for fighting cancer

By Krista Conger

Fighting off cancer requires the concerted efforts of immune molecules throughout the body, rather than just in the tumor itself, according to a new study of laboratory mice by researchers at the Stanford University School of Medicine.

The finding helps settle an ongoing dispute among clinicians as to whether systemic, or whole-body, responses are as important as a robust response by immune cells in the tumor itself. The study may help clinicians understand why some people with cancer respond favorably to cancer immunotherapy, while others experience little or no benefit. It also suggests ways that the effectiveness of ongoing therapies could be quickly and easily monitored.

“Immunotherapy can be remarkably effective against cancer, but we don’t know why some patients respond and some don’t,” said Edgar Engleman, MD, professor of pathology and of medicine. “We don’t understand the parameters that determine success or failure. In this study, we analyzed millions of living cells simultaneously for 40 parameters from multiple tissues throughout the body to show that there is a systemwide immune response to effectively attack and eradicate a tumor.”

Engleman is the senior author of the study, which was published online Jan. 19 in Cell. The lead authors are Matthew Spitzer, PhD, a former Stanford graduate student who is now a postdoctoral scholar at UC-San Francisco; former Stanford postdoctoral scholar Yaron Carmi, PhD, who is now an assistant professor at Tel Aviv University; and Stanford postdoctoral scholar Nathan Reticker-Flynn, PhD.

Infammation continued from page 1

also a Howard Hughes Medical Institute investigator.

Caffeine link

“Our findings show that an underlying inflammatory process, which is associated with aging, is not only driven by cancer but is, in turn, driven by molecular events that we may be able to target and combat,” said Davis, who holds the Burt and Marion Avery Family Professorship.

For the new study, the researchers compared blood drawn from older and younger study participants to see which genes tended to be more highly activated in older people. They zeroed in on two clusters of genes whose activity was associated with the production of a potent circulating inflammatory cytokine called IL-1-beta. The genes within each cluster appeared to work in coordination with one another.

The researchers also looked at two particular groups of older participants: One with high activation of one or both inflammatory gene clusters, and the other with one or both clusters exhibiting low activation. On reviewing these individuals’ medical histories, the scientists learned that nine of the 12 subjects with high cluster activity had high blood pressure, compared with only one of the 11 subjects with low cluster activity.

Follow-up studies by study co-author Francois Hadj-Mc, MD, a clinical associate professor of cardiovascular medicine, revealed that individuals in the “high” group were much more likely to have stiffer arteries — a risk factor for cardiovascular complications — than those in the “low” group.

Furthermore, those in the low group were eight times as likely as those in the high group to report having three days of high blood pressure, compared with only one of the 11 subjects with low cluster activity.

New research continues to show the immunologic benefits of caffeine, a very plausible mechanism for why this might be so.”

How caffeine may affect longevity

Intrigued by the correlation between older participants’ health, gene-cluster activation and self-reported rates of caffeine consumption, the researchers followed up and verified that blood from the group with lower caffeine consumption was enriched for and a number of its metabolites, compared with blood from the group with higher cluster activity. (Examples of these metabolites are theophylline, also found in tea, and thebrosine, which abounds in chocolate.)

Incubating immune cells with caffeine and its breakdown products along with the inflammation-triggering nucleic acid metabolites substantially prevented the latter from exerting their powerful inflammatory effect on the cells. “That something many people drink — and actually like to drink — might have a direct benefit came as a surprise to us,” said Davis, who noted that the study didn’t prove a causal link. “We didn’t give some of the mice coffee and the others decaf. What we’ve shown is a correlation between caffeine consumption and long-lived mice, and we’re very interested in the preclinical tests, a very plausible mechanism for why this might be so.”

Other Stanford co-authors are postdoctoral scholars Junlei Chang, PhD, Christopher Bohlen, PhD, and Gabriela Fragiadakis, PhD; former graduate student Matthew Spitzer, PhD; life science research associate Edward Cao; assistant professor of anesthesiology, peripertative and pain medicine Brice Gaudilliere, MD, PhD; professor of microbiology and immunology Garry No- an, PhD, and Gauthier P. Vezen, PhD; and Brice Gaudilliere, MD, PhD.

Researchers from the Sidra Medical and Research Center in Qatar, the French National Institute of Health and Medical Research and the University of North Carolina also co-authored the study.

The research was supported by the National Institute of Allergy and Infectious Diseases and the Ellison Medical Foundation.

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

In mice that received effective therapy, this finding is important because the rise in these CD4 T cells may prove useful as an indicator of treatment efficacy and could spur the development of new forms of immunotherapy, thus allowing researchers and clinicians to develop a way to more accurately monitor the effectiveness of therapies. See IMMUNE, page 8

Physicians could learn quickly whether a therapy is working.

Two-pronged approach

The researchers compared the immune responses of a special group of laboratory mice engineered to spontaneously develop two types of brain cancer. These cancers are resistant to a type of immunotherapy known as checkpoint blockade. Recently, however, Engleman and his colleagues showed that they could stimulate a successful immune response and eradicate tumors in the animals with a reengineered approach that incorporated both a tumor-binding antibody and molecules that activated a type of immune cell called a dendritic cell. In this finding, they allowed us to directly compare the responses to two immunotherapies,” said Engleman. “What’s going on in an effective response that’s not happening in the ineffective response? What we found was quite revealing and surprising.”

Spitzer, Carmi and their colleagues collaborated with co-author Garry No-an, PhD; a professor of microbiology and immunology at Stanford who has developed a way to use a technique known as mass cytometry to monitor the physical attributes of individual cells in samples of millions or billions. This allows researchers to piece together a dynamic view of how multiple cell populations respond in real time to changing conditions like disease or drug therapies.

Spitzer and his colleagues used the technology to monitor the rise and fall of various populations of immune cells within the tumor as well as in other tissues — including the lymph nodes, spleen, bone marrow and peripheral blood — over time. They found that, immediately after immunotherapy and through-out tumor rejection, the researchers found that animals treated with the effective, two-pronged approach, the prevalence of immune cells including macrophages, dendritic cells and T cells — in the tumor itself increased dramatically within a period known as “priming.” These cells also divided more rapidly. In contrast, the turnover of the animals receiving the ineffective therapy, checkpoint blockade, displayed no such increase in prevalence or proliferation.

Increase in regulatory T cells

Importantly, the researchers also observed a five-fold increase in a class of cells called regulatory T cells in the effectively treated animals during priming. The finding of these specific immune responses was surprising because they have in the past been correlated with a negative prognosis for many tumors.

“Our observation of an increase in the prevalence of these cells in successfully treated tumors runs counter to conventional wisdom and points out the complex nature of the immune response that lead to successful immunotherapy,” said Engleman.

Tumor rejection in the effectively treated animals began by day eight. However, in contrast to the priming phase, the researchers observed no differences in the number of immune cell proliferations in tumors between the two groups of animals during rejection. In fact, the immune response occurring this time. In fact, immune cell proliferation — that activated a type called regulatory T cells in the effectively treated animals — was much more likely to have occurred in the tumor itself. Moreover, the researchers were able to show that some of these specific changes in the activity and prevalence of immune cells in the peripheral blood.

“This finding is important because the rise in these CD4 T cells may prove useful as an indicator of treatment efficacy and could spur the development of new forms of immunotherapy, thus allowing researchers and clinicians to develop a way to more accurately monitor the effectiveness of therapies. See IMMUNE, page 8

Edgar Engleman is the senior author of a study that found a systemwide immune response is needed to effectively attack a tumor.

The researchers made this discovery using data drawn from older versus younger study participants to compare the responses of immune molecules within the tumor as well as in other tissues — including the lymph nodes, spleen, bone marrow and peripheral blood — over time. They found that, immediately after immunotherapy and through-out tumor rejection, the researchers found that animals treated with the effective, two-pronged approach, the prevalence of immune cells including macrophages, dendritic cells and T cells — in the tumor itself increased dramatically within a period known as “priming.” These cells also divided more rapidly. In contrast, the turnover of the animals receiving the ineffective therapy, checkpoint blockade, displayed no such increase in prevalence or proliferation.

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Edgar Engleman is the senior author of a study that found a systemwide immune response is needed to effectively attack a tumor.
"The trick was to use a compound that blocks pain receptors only in the periphery."
Leslie Subak, MD, has been appointed the chair of the Department of Obstetrics and Gynecology at the School of Medicine, effective Dec. 1. Subak will succeed Jonathan Berek, MD, the Laurie Kraus Lacob Professor, who has served as chair of the department since 2005.

Subak earned her medical degree at Stanford in 1991 and went on to a distinguished career as a scientist, clinician and educator at the University of California-San Francisco, where she’s now a professor of obstetrics, gynecology and reproductive sciences, epidemiology and biostatistics, and of urology. She is an expert in urogynecology and pelvic surgery, and the principal investigator for federally funded research projects on the epidemiology of urinary incontinence in women, evaluating treatments for urinary incontinence.

“Leslie has made indispensable contributions to the fields of obstetrics and gynecology,” said Lloyd Minor, MD, dean of the School of Medicine, in a statement announcing the appointment. “Her astute leadership of major clinical and translational research programs has led to fundamental discoveries in many areas of women’s health, and her own scientific investigations have significantly advanced the treatment of women suffering from urinary incontinence.

Subak’s research has focused on multidisciplinary approaches to treating incontinence in women, including cooperation between basic and clinical investigators researching the female bladder, pelvic floor and urethra; and among clinicians and experts in epidemiology and biostatistics. This is an area of vital economic impact and has shown that weight loss can be an effective treatment for the condition.

Subak is also dedicated to training the next generation of leaders in women’s health, running fellowship and junior faculty K-12 training programs.

Excited about return to Stanford

“I look forward to helping each member of the department to thrive in her or his unique career path,” she said in an email.

“Tumors from eventually growing.

The importance of the systemic immune response was validated when the researchers gave the mice a tumor burden. The immunity of immune T cells to migrate from secondary lymphoid organs, such as the lymph nodes and spleen, to the tumor site. This intervention allowed sustained tumor growth even in the absence of a previously effective treatment.

In the past, researchers focused on understanding in minute detail what is happening at the molecular level in immune cells inside the tumor,” said Engleman. “But we took an approach that allowed us to zoom out and look at the immune system as a whole. This enabled us to unravel unique patterns of activity that could be either tumor protective or promoting.

In addition to finding cancer therapy, the researchers also believe the technique could be useful in tracking the changes that occur during an autoimmune disease flare, or to learn more about how the body marshals its forces to fight off an infection.

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.

Other Stanford co-authors are former life sciences technicians Jonathan Chabon; and assistant professor of medicine and neurology with a focus on neuro-ophthalmology, including the diagnosis and treatment of brain, nerve and muscle disorders that affect vision.

JOHN LEPPERT, MD, was promoted to associate professor of urology, effective Nov. 1. His research and clinical work focuses on kidney cancer surgery, kidney cancer detection and responses to cancer therapy.

S.V. MAHADEVAN, MD, was promoted to professor of emergency medicine, effective Dec. 1. He is the interim chair of emergency medicine. His research and clinical interests include emergency medicine education, trauma, emergency medical services and global health.

ELIZABETH MORRINO, PhD, was appointed associate professor of otolaryngology-head and neck surgery, effective Nov. 1. He is a pediatric otolaryngologist with research interests in the prevention of ototoxicity, neonatal hearing screening, the genetics of hearing loss and pediatric cochlear implants.

KOREY HOOD, PhD, was appointed professor of pediatrics and of psychiatry and behavioral sciences, effective Nov. 1. His research focuses on neuro-ophthalmology, including the diagnosis and treatment of brain, nerve and muscle disorders that affect vision.

HEATHER MOSS, MD, PhD, was appointed professor of ophthalmology, effective Nov. 1. Her research aims to identify and develop makers of impaired optic nerve structure and function that can guide management of idiopathic intracranial hypertension to prevent blindness. Her clinical focus is on neuro-ophthalmoLOGY, including the diagnosis and treatment of brain, nerve and muscle disorders.

JOCHEN PROFIT, MD, was promoted to associate professor of pediatrics, effective Dec. 1. His clinical focus is on neuro-oncology, including the diagnosis and treatment of brain, nerve and muscle disorders.

HUA TANG, PhD, was promoted to professor of genetics, effective Dec. 1. In her research, she develops statistical and computational approaches to delineate the evolutionary history of the human population and to examine the genetic architecture of complex traits and diseases in minority populations.

WEN-KAI WENG, MD, PhD, was promoted to associate professor of medicine, effective Dec. 1. His clinical focus is blood and marrow transplantation, and his research focuses on lymphoma, including immunotherapy and efforts to understand its pathobiology.