Study pinpoints how X chromosome silenced

By Krista Conger

Garfield has a dark secret. The cartoon cat is a genetic anomaly, not because of his insatiable lasagna cravings, but because of his coat color. Outside the world of the Sunday comics, orange and black cats are almost invariably female.

This truism is due to a curious biological phenomenon called X inactivation, which ensures that females of all species have only one active X chromosome in every cell. Early in development, when embryos have just few cells, one X chromosome is shut down or silenced in each cell. This chromosome remains inactive in all of that cell’s progeny throughout the life of the animal. In cats and many other species, the selection of the chromosome to be inactive is random; in some other species, the X chromosome inherited from the father is always chosen.

X inactivation is necessary to ensure that females, who have two X chromosomes, and males, who have only one, end up with roughly the same dosage of genes that occur on that chromosome. The “orange or black fur” gene is on the X chromosome, so a female cat can have a calico coat with both colors if “orange” and “black” remain active in different cells, but because a male cat has just one X chromosome it can be only one of these colors.

Scientists have known about X inactivation for decades. Recently they learned that an RNA molecule called Xist is responsible. But it’s not been as easy to figure out exactly how Xist works to silence genes on the X chromosome.

Now researchers at the School of Medicine have outlined the molecular steps of inactivation, showing that it occurs in an orderly and directed fashion as early embryonic cells begin to differentiate into more specialized tissues. They’ve identified more than 80 proteins in mouse cells that bind to Xist to help it do its job.

“Gender differences in diseases”

“We see some very interesting phenomena with X-linked diseases in humans,” said Howard Chang, MD, PhD, professor of dermatology. “Often, when the faulty gene is on the X chromosome, the condition is more severe in hemophilia, for example. In contrast, women are far more likely than men to suffer from autoimmune diseases, for reasons we don’t yet understand. This research opens the door to possibly understanding the biological basis for these differences.”

A paper describing the research findings was published in the April 9 issue of Cell. Chang is the senior author, and former graduate student Ci Chu, PhD, is the study’s lead author. The research required an entirely new technique, which was developed by Chu, to identify proteins interacting with Xist.

“Usually people start with a protein of interest and look for RNA molecules that might associate with that protein. We wanted to start with the RNA and find out what proteins Xist is interacting with.”

Researchers identify major cellular culprit in scarring

By Krista Conger

A small cell responsible for scarring, and a molecule that inhibits the cell’s activity, have been identified by researchers at the School of Medicine.

The molecule slowed wound healing in mice but alleviated scarring, the researchers said.

The researchers also found that the cell may play a role in the growth of melanoma and in skin damage caused by radiation. A drug that acts in the same way as the inhibitory molecule is already approved for use in humans as a treatment for type-2 diabetes, so it could potentially move quickly into clinical trials for the treatment of scarring and melanoma.

“The biomedical burden of scarring is enormous,” said Michael Longaker, MD, co-director of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine. “About 80 million incisions a year in this country heal with a scar. That’s why Xist and the other proteins we’ve identified are so important.”

A genetic phenomenon called X inactivation is the reason that most calico cats are female. Now researchers have outlined the molecular steps of inactivation, showing that it occurs in an orderly and directed fashion as early embryonic cells begin to differentiate.

Scientists decipher brain’s noise

By Bruce Goldman

By directly recording electrical activity from the human brain, neuroscientists at the School of Medicine have shown that distinct, distant groups of brain areas that support memory retrieval persist throughout our cycles of waking and sleeping.

The findings, described in a study published online April 8 in Neuron, confirm for the first time that specific electrical patterns of coordinated neural activity in widely separated human brain structures during memory retrieval persist throughout our cycles of waking and sleeping. The findings confirm indirect observations made in previous studies that used brain imaging. They also shed light on why the brain paradoxically appears to exhaust so much of the body’s energy in what, at first glance, seems akin to the idling of a car’s engine.

The human brain is a greedy organ. Accounting for only 2 percent of the body’s weight, it consumes 20 percent of the body’s energy. Yet the rate at which the brain gobbles glucose (the fuel our brain cells run on) barely budges when we cease performing a physical or mental activity. Even at rest, the brain seems engaged in a blizzard of electrical activity, which neuroscientists have historically viewed as useless “noise.”

“Increases in brain activity during conscious thoughts and actions represent only the tip of the iceberg,” said Josef Parvizi, MD, PhD, associate professor of neurology and neurological sciences and the senior author of the Neuron study. “The vast amount of energy consumption by our brain is due to its spontaneous activity at all times when we are not consciously involved in a specific task.”

What, then, is all this spontaneous noise for? At rest, but not resting

Over the past decade, neuroscientists using brain-imaging methods like functional MRI scans, which track blood flow in the brain (believed to be a good stand-in for local neural activity), have started to reveal

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Stanford Center for Clinical and Translational Medicine. "Mark Cullen is the right man for the job," said Lloyd Minor, MD, dean of the School of Medicine at Stanford, and chief of the Division of General Medical Disciplines at Stanford, is bringing groundbreaking occupational health research to improve its employees' health. Back then, he partnered with Alcoa, America's largest aluminum producer, to research ways to improve its employees' health. Back then, it took him five years to create data bridges between the company's hundreds of thousands of fragmented health, employment, and injury and environmental records. "Our goal was to understand factors that undermine worker health, then to develop prevention and treatment strategies," he said. This research led to groundbreaking occupational health reforms, including environmental controls and new strategies to reduce injury and illness. It was eye-opening to discover that other aspects of work and life — not just toxins and bad behavior — conspire to produce positive and negative outcomes. When I witnessed how multidisciplinary teams could unlock knowledge hidden within population data, I was hooked.

Now Cullen, professor of medicine and chair of the Division of General Medical Disciplines at Stanford, is bringing his experience and enthusiasm to the Stanford Center for Population Health Sciences as its first director. "Backed by Stanford's research and computational engines, the Center for Population Health Sciences is poised to harness the power of big data to improve health here and around the world," said Lloyd Minor, MD, dean of the School of Medicine. "Mark Cullen is the right person to bring together clinicians and researchers in social, biologic and data sciences to meet these challenges."

Population health science mission

Launched in 2012 by Spectrum, the Stanford Center for Clinical and Translational Research and Education, the center's mission is to use population-level evidence to improve bedside care and the overall health of society. This evidence can come from a variety of sources — electronic medical records, genomic sequences, biospecimen repositories, insurance records, wearable sensors and social and environmental data. The challenge is to create methods to deliver this information to researchers and care providers in relevant and privacy-protected formats.

This isn't rocket science, but there were no financial incentives to develop these tools until the Accountable Care Act came along," said Cullen.

The 2010 Patient Protection and Affordable Care Act includes cost-reduction and quality-improvement incentives that health-care institutions can take advantage of through the wise use of population-health data. These are incentives for hospitals that show improved outcomes for heart failure, pneumonia and surgery. And there are incentives for clinicians and hospitals to set up accountable care organizations to lower annual per-capita growth on health spending and improve health for large populations.

Population-health scientists can be instrumental in creating the tools to more effectively and efficiently help institutions take advantage of these quality-focused incentives, said Cullen. During the last year, Lorene Nelson, PhD, associate professor of health research policy and the center's associate director, helped lay the foundation for the center, engaging more than 200 faculty members in a series of meetings and symposia. With the assistance of Spectrum staff, she also organized a distinguished lecture series to bring new ideas to the Stanford community, launched a website and Twitter feed to foster collaborations, and expanded the pilot program.

To date, the center has awarded 26 project teams with grant awards ranging from $20,000 to $50,000. Funded by Spectrum's Clinical and Translational Science Award from the National Institutes of Health and by Stanford Health Care, many of these projects are focused on developing a "learning health system," in which clinical data can be linked to evidence information relevant to patient health, such as neighborhood locations and environmental conditions. Representations of these projects include:

- Design of an electronic clinical-decision support system to improve emerging care for children.
- Development of a personalized medicine practice using genomic data.
- Methodologies for using Google Street View to assess neighborhoods for population health research.
- "Today's electronic medical records are a snapshot of many years ago — let's provide a snapshot of a chart without much added value," said Cullen. "We want to add intelligence to medical records in the same way that smartphone navigation apps have added real-time traffic alerts and alternate routes. For example, when an asthmatic child comes to the emergency department, a physician's dashboard might include information on air quality, viral outbreaks in the patient's neighborhood and the child's vaccination record.

Access to new data, populations

To better support the efforts of population-health scientists, the center is working on provincially. It has a number of partnerships, including exclusive testing by the Boston-based Partners Health System and Google Earth, and access to a variety of U.S. and international health databases. Stanford population scientists are now using or envision using these databases to address millions of questions.

- To understand the complex financial, social and regional incentives that drive health-care delivery in the United States, researchers are testing and generating detailed information on what types of services patients are using, where they are using them and how much they cost," said Kate Bendifor, MBA, MPH, PhD, associate professor of health research and policy. "Developing a large repository of insurance claims will enable Stanford researchers to examine these types of questions.

The center plans to make these data sets available at very low cost to Stanford trainees and investigators at every level. But even more important, center staff will provide technical support to help researchers get access to the data needed to answer their research questions. Other data sets the center hopes to make available over time include those from the Google X Baseline Study and Inception Network.

The Google study is a five-year pilot study in which daily health information is collected from 500,000 adults living in Southern California via a Google-designed web portal and with biometric services, such as glucose-measuring contact lenses and activity-measuring accelerometers. The study's objective is to provide researchers with a comprehensive picture of human health and the transition to disease. Collaborators include the Stanford School of Medicine and Duke University School of Medicine. Baseline studies have just begun.

Inception Network is a coalition of health and demographic surveillance systems in 23 low- and middle-income countries in Africa and Asia. Negotiations are underway to enable Stanford researchers to initiate collaborative studies on geographically defined groups under regular surveillance by local scientific teams.

In addition to large data sets, the center is developing easier access to clinical, administrative and other segmented study populations. With the databases, center staff will work with investigators to identify connections between population groups that could be of importance to their research.

Nationwide clinical data access

Population-health researchers can also look forward to enhancements to STIRIDE, the Stanford Translational Research Integrated Data Environment, a comprehensive warehouse of de-identified clinical notes, diagnoses and prescriptions for nearly 2 million patients treated since 1994 at Stanford Hospital and Clinics, Stanford Health Care, and Lucile Packard Children's Hospital Stanford.

Michael Halasa, chief information officer for the School of Medicine, has led the effort, initiated by Spectrum and other member institutions in the CTSA consortium, to connect STIRIDE to a nationwide, scalable informatics framework called i2b2. When this project is complete, Stanford researchers will be able to access anonymized clinical data from participating health-care systems around the country for research and clinical trial recruitment. The i2b2 framework is based on the Research Patient Data Registry developed at Massachusetts General Hospital.

"I couldn't be more pleased with the tremendous progress that all the faculty who have worked on this initiative have made over the last two years," said Gary Greenberg, MD, senior associate dean of research for the medical school and director of Spectrum. "With the appointment of Mark Cullen, the center is poised to take the next step in becoming a hub for research and engagement in activities related to population health across the university. Perhaps most exciting to me, with all the talent we have at Stanford, we will be able to provide much-needed guidance to investigators, clinicians and policy makers concerning the very difficult task of drawing accurate inferences from the great wealth of new data now available at our fingertips. This data has the potential to inform and well-being of local, national and even global populations."

Mark Cullen has been named the first director of the Center for Population Health Sciences, whose mission is to use population-level evidence to improve bedside care and the overall health of society. Population-health researchers can benefit from the new center that involves the potential to improve the health and well-being of local, national and even global populations."

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

In the largest study of its kind to date, researchers at the School of Medicine and their colleagues have found that worldwide only a limited number of mutations are responsible for most cases of transmission of drug-resistant HIV.

HIV, the virus that causes AIDS, can mutate in the presence of antiviral drugs, and these mutations can be transmitted from one person to the next.

In the new study of more than 50,000 patients in 111 countries, the researchers found a small group of mutations accounted for a majority of the cases of transmission-related resistance to the HIV drugs used to treat infections in resource-limited settings. The results suggest the levels of transmission of drug-resistant strains have not increased globally as much as once feared, said Robert Shafer, MD, professor of medicine and principal investigator for the study.

“What we are showing is that the rates of transmitted drug-resistant HIV in the low- and middle-income countries most affected by HIV have increased modestly. The rate of increase in sub-Saharan Africa has been low, and an increase has not been detected in south Asia and Southeast Asia. That’s good news,” Shafer said.

However, there continues to be an increase in drug resistance because the regimens used by HIV patients in lower-income countries are often not as robust as those used in upper-income countries, and strict adherence to regimens of six months or longer is challenging, particularly for people in the poorest parts of the world, he noted. “It is inevitable that transmitted drug resistance will increase further, so we need to continue ongoing monitoring to ensure successful, long-term treatment outcomes for the millions of people on therapy world-wide,” Shafer said.

He said the findings could have important implications for treatment in these high-burden regions, leading to the development of an inexpensive test for key mutations to help determine which drugs should be given to previously untreated patients.

The study was published online April 7 in PLoS Medicine.

Halting the spread of HIV

To gauge the extent of the problem of transmitted resistance to HIV drugs, Shafer and his colleagues reviewed HIV sequencing data on 50,870 individuals across the globe, taken from 287 studies published between 2000 and 2013. Nearly 60 medical institutions on five continents contributed data for the study. The researchers analyzed each virus sequence for the presence of 93 mutations previously shown to be indicators of drug resistance.

They found the overall prevalence of transmitted drug resistance ranged from 2.8 percent in sub-Saharan Africa to 11.5 percent in North America. In south Asia and Southeast Asia, the prevalence of transmitted resistance remained unchanged during the decade of expansion in drug treatment. However, many studies from sub-Saharan Africa have shown the prevalence of resistance to be more than 5 percent in recent years, Shafer noted. He said the inevitable increase in transmitted drug resistance could undermine confidence in the ability to treat HIV in low-income regions and potentially dissuade new patients from seeking care.

To avoid that prospect, the study points to the possibility of creating a simple, inexpensive test for the key resistance-related mutations, which could help clinicians pinpoint the drugs likely to be most effective for individual patients. In both Africa and Asia, the researchers identified four specific resistance mutations that were associated with the drugs nevirapine and efavirenz. These are among an older, less-expensive class of drugs known as non-nucleoside inhibitors, typically used in the developing world as part of a standard, daily regimen.

“The idea of an inexpensive test for key mutations is attractive because if it were used in conjunction with a viral load test [a measure of the amount of virus in a patient’s blood], it would allow physicians to know if therapy should be changed and whether counseling should be given,” Shafer said. Patients who show signs of these mutations could be switched to newer, albeit more costly, but more potent drug inhibitors, which are less susceptible to resistance, he said.

“You could therefore shut off the flow of drug resistance by using regimens that don’t develop drug resistance and target the development of drug resistance in the first place,” he said.

Unrelated strains

The study also found that the drug-resistant strains did not come from a single line of resistant viruses, but were distinctly different from each other, suggesting they had been acquired independently and not as a result of a single transmission chain. That contrasts with patterns of resistance in other microbes, such as malaria and tuberculosis, where resistant strains tend to move rapidly among populations, Shafer said. It also contrasts with patterns in many upper-income countries, where 20 years of HIV therapy have spawned the spread of many highly drug-resistant strains.

“We are finding that the strains being detected in low-income countries are pretty much unrelated to one another. So that suggests these have not yet gained a foothold in the population, and are less often being transmitted among people who have never received the drugs before,” Shafer said.

Other Stanford co-authors are Soo-Yoon Rhee, MA, a research associate and first author of the study; John Ioannidis, MD, DSc, professor of medicine and of health research and policy; Jonathan Taylor, PhD, professor of statistics; J. Michael Goedert, MD, PhD, James Walsh, PhD, and Nevin Agis, PhD, of applied physics at Stanford, who is the senior author; and Jonathan Hardcastle, and lead to larger errors.

The work was funded by the National Institutes of Health, the Bill & Melinda Gates Foundation and the Center for AIDS Research.

Stanford’s Department of Medicine also supported the work.

Few mutations involved in transmission of drug-resistant HIV

By Kim Smuga-Otto

By analyzing the activity of "GPS" neurons in mice, researchers at the School of Medicine have discovered that the mental maps created by these cells accumulate errors, which are corrected when the animal encounters a wall.

This supports the theory that these cells, called grid cells, use an animal's perceived speed and direction to help it navigate familiar places.

But grid cells can make small errors, said the Stanford researchers, adding that the animal's memory of its trajectory Feurich, PhD, is a science-writing intern;

Researchers Vici Varghese, Robert Shafer and Soo-Yoon Rhee are co-authors of a paper that found that a small group of mutations accounted for a majority of the cases of transmission-related resistance to HIV drugs used to treat infections in developing countries.

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Earl Shook knew he was in trouble. He couldn’t walk five feet without losing his breath and stopping to rest. He couldn’t carry his 35-pound bag of food without dropping it to the floor. And he couldn’t cook for the Fifty Plus Club at the Menlo Park Presbyterian Church, where he worked.

For weeks, Shook, 74, had been experiencing shortness of breath, which his physician treated as pneumonia. As his condition worsened, he returned to the doctor, but needed a wheelchair to get from his car to her office. She knew immediately there was something else going on, and sent him to a cardiologist for a consultation. Shook was diagnosed with congestive heart failure with atrial fibrillation, and was told that he should be hospitalized. Shook resisted, convincing his doctor to let him cook for the Fifty Plus Club that Friday night. But when he could barely stand with both hands holding onto a table, he and everyone around him knew he needed help.

He was transported via ambulance to Stanford Hospital from his cardiologist’s office the following Monday, and spent a week in the hospital.

At discharge, Shook became one of the first people to be enrolled in a pilot project that monitors heart-failure patients at home. Launched earlier this year, the project is a joint effort of Stanford Health Care’s heart failure team and Aging Adults Services Program. Nursing & Rehab at Home, an SHC community partner, are collaborating on the project. The goal is to teach these at-risk patients self-management of their chronic condition, and keep them from being admitted to the hospital.

“There is abundant evidence in the literature that suggests home monitoring can improve patient outcomes,” said Rta Ghatak, PhD, director of Aging Adults Services. “It can improve survival, days out of the hospital, quality of life, and it provides an extra measure of psychosocial support.”

According to project leader Dipanjan Banerjee, MD, clinical assistant professor of cardiovascular medicine, Stanford has employed a number of interventions to reduce heart-failure readmissions over the past three years, but they have all been inpatient, hospital-based interventions, such as scheduling follow-up appointments prior to discharge, making discharge phone calls, educating patients about managing their condition at home, and reconciling medications before discharge.

“All of these are great interventions, but they don’t speak to what happens to the patient at home,” said Banerjee, who is also director of SHC’s Mechanical Circulatory Support Program. “There’s a big opportunity to use home monitoring or home-based approaches to improve patient care.”

Bringing care home

A day after arriving home, Shook received a digital scale, a blood pressure cuff, a pulse oximeter and a hub station and was trained on using the devices by the Nursing & Rehab at Home staff. For 30 days, Shook weighed himself daily and took his blood pressure and oxygen saturation. His readings were automatically transmitted to a central monitoring portal. If he skipped a day, the home health agency would call to remind him. If his vital signs were out of the normal range, the agency would contact the Stanford nurses to intervene.

“A key focus in heart failure management is prompt symptom recognition and knowing what action to take when early signs of decompensation emerge,” said Christine Thompson, RN, clinical nurse specialist for the heart failure team, who helped develop the pilot project. “Daily monitoring of vital signs, in addition to assessment of subjective symptoms, is a tool that may particularly benefit some of our high-risk patients.”

As part of the project, patients also receive a home visit by one of four Aging Adult Services nurses — Pauline Marchon, RN, Terese McManis, RN, Candece Mindigo, RN; or Lourina Co, RN. In addition to ensuring that patients are using the monitoring equipment correctly, the home visit allows the nurses to reinforce messages about diet, exercise and medications. On more than one occasion, these visits uncoved a potential health problem that could be addressed immediately.

When McManis conducted a home visit with Shook, she noticed something was awry. His blood pressure readings were abnormal, she said, and his diastolic number, at 110, was very high. The nurse was concerned enough to call Thompson. “We got him in to see his cardiologist the next day,” said McManis. His medications were adjusted immediately, bringing his blood pressure back into a normal range within two days.

Heart failure is a complex syndrome requiring lifelong adherence to medications and certain dietary restrictions, as well as daily self-assessment of symptoms, Ghatak said.

“Heart failure doesn’t end when patients leave the hospital,” said Angela Bingham, RN, nurse coordinator for the heart failure team. “A big part of managing heart failure is teaching self-management for patients with chronic disease. The home monitoring pilot really supports patients doing that.”

“There’s a big opportunity to use home monitoring or home-based approaches to improve patient care.”

Providing peace of mind

The pilot project plans to enroll 30 patients with heart failure from the inpatient and clinic settings, and provide them with home monitoring equipment for 30 days free of charge. To date, it has enrolled 22 patients. Not every heart failure patient is a candidate, Bingham said. Patients must live within Santa Clara and San Mateo counties, and be well enough to conduct the self-monitoring or have someone in the home available to help them. At this time, patients must also speak English or have someone who can interpret for them in their home. At the end of the 30-day monitoring period, a nurse conducts a phone survey to evaluate the program’s impact on the patient’s health and quality of life.

For Shook, being sent home after a week in the hospital was unnerving. “When you’re cared for at the hospital by good nurses and doctors, and you’re sent out from the hospital, there’s a void,” he said. The home monitoring was reassuring, he added. “It let me know there was somebody there still caring for me.”

Shook has completed the 30 days of being monitored, but still chooses to monitor himself daily with equipment he acquired on his own. A lifelong chef who cooked for the airlines at San Francisco International Airport for much of his career, Shook has had to learn a whole new way to cook,” he said, cutting back dramatically to manage his high blood pressure, and using herbs, lemon and mustard to season his food.

“Seeing those numbers every day helped me change my diet,” he said. “I’d lose a little more weight every day,” he said. “It gave me a sense of discipline. Now I make sure to take all my pills. Before I would skip them sometimes.”

Grace Hammerstrom is a freelance writer for Stanford Health Care.

By Bruce Goldman

The 2015 Big Data in Biomedicine Conference, to be held May 20–22 at the School of Medicine’s Li Ka Shing Center for Learning & Knowledge, will bring together hundreds of participants from around the world to discuss ways of harnessing the power of big data to improve human health. More than 1,000 others watched the event online via live-streamed video.

Topics to be highlighted this year will include genomics, neuroimaging, crowdsourcing, statis- tics, ethical and legal issues, immunol- ogy and “learning” health systems.

The research of one of the keynote speakers, Michael Levitt, PhD, professor of structural biology at Stanford, exemplifies the revelations made possible through the application of computer power to biomedical problems. Levitt shared the 2013 Nobel Prize in Chemis- try for his development of multi-scale models elucidating the conformations of huge, unwieldy biomolecules.

Other keynote speakers will be Sha- nnon Levy, CEO of Genetic Alliance; Kathy Hudson, PhD, deputy direc-
Adherence to blood thinner best with pharmacist management

By Tracie White

Patients are more likely to take a new type of blood thinner correctly and without missing doses when they are managed by pharmacists, rather than only by doctors or nurses, according to a study co-authored by a researcher at the School of Medicine.

Mintu Turakhia, MD, assistant professor of medicine, and fellow researchers studied a new treatment for atrial fibrillation, a dangerous heart disorder that increases the risk of stroke and blood clots. The treatment, a drug called dabigatran, is one of a new class of twice-daily oral medications. A paper describing the findings was published April 14 in the Journal of the American Medical Association.

Researchers found that Veterans Health Administration patients who got their prescriptions for the medication filled by VHA pharmacists who educated them about the drug and checked their adherence on a regular basis were 80 percent more likely to follow medication guidelines than those who didn’t receive this kind of support.

“The new oral anticoagulants, such as dabigatran, represent a dramatic medical change in the delivery of care for a-fib patients,” said Turakhia, the senior author of the study. “Before, the only option was lifelong blood thinners such as warfarin, which is cumbersome and requires blood testing once or more per month.”

What leads to better adherence

Because these new drugs come in fixed doses and patients taking them don’t need to undergo regular blood tests, health-care professionals assumed that the drugs wouldn’t need to be monitored as closely. What this study shows is that when the drug was delivered by pharmacists who provided an increased level of patient support, patient adherence greatly improved.

“Although pharmacist-led management of these new drugs is uncommon in the U.S., the findings make the case that it is still important and can ultimately impact clinical outcomes,” Turakhia said.

Since the first of the new drugs was approved by the Federal Drug Administration (FDA) in 2010, physicians have been increasingly prescribing them in place of warfarin, an anticoagulant that has been used for more than 50 years, Turakhia said. Evidence shows that the new drugs work as well at least as warfarin, and cause less bleeding — but only when taken correctly. “This is important because even missing a few doses can lead to acute events such as stroke,” he said. “How well you take the new drugs largely determines your treatment benefit.”

The new oral anticoagulants are popular with many patients because they require no more than one visit to measure their levels in the blood. Patients are instead simply sent home from the pharmacy with the pills.

Alternative to warfarin

“Among my patients, I used to get asked about alternatives to warfarin dozens times a week,” Turakhia said. “Many of them were unhappy with the need for regular, often lifelong blood testing.”

Atrial fibrillation, a type of heart arrhythmia, is a common and growing problem in the United States that affects at least 3 million people. Due to rising rates of obesity and hypertension, that number is increasing, and more young people at a younger age are developing the disorder. A-fib may result in symptoms such as palpitations, racing heart, shortness of breath, or warfarin failure. An irregular heartbeat leads to poor blood flow, which puts patients at a high risk of stroke.

The introduction of these new blood thinners has been a major change in the treatment plan for many of these patients.

According to the FDA, from its approval in October 2010 through August 2012, about 3.7 million prescriptions for dabigatran (Pradaxa) were dispensed, and approximately 725,000 patients received a dispensed prescription from U.S. outpatient retail pharmacies.

Heart researchers became concerned when studies began showing that patients were not adhering as well to treatment guidelines with this new blood thinner, in some cases crippling the treatment’s effectiveness, Turakhia said.

Puzzled by this, researchers set out to determine if this lack of adherence could be explained by where patients were filling their prescriptions for the medication. They looked at Veterans Health Administration sites where 20 or more outpatients had dabigatran prescriptions filled between 2010 and 2012.

“Surprisingly, we found that treatment adherence varied not by individual, but by site,” said Turakhia, who is also a cardiac electrophysiologist at Stanford Health Care and the Veterans Affairs Palo Alto Health Care System. “We didn’t expect to see that much variation by site.” Next, researchers conducted in-depth telephone interviews with the managers, usually pharmacists, at 41 of these pharmacy sites.

“We rolled up our sleeves and looked at what each site was doing,” Turakhia said.

Benefits of supportive pharmacist

At the sites with the highest patient adherence, there was usually a pharmacist actively educating patients on medication adherence, reviewing any possible drug interactions, and following up to anticipate refills and get patient their refills promptly before medications run out.

“We’re suggesting that greater structured management of these patients, beyond the doctor just prescribing medications for them, is a good idea,” Turakhia said. “Extra support, like that provided in the VA anticoagulation clinic with supportive pharmacist care, greatly improves medication adherence.”

The lead author of the study, Supriya Shore, MD, is a cardiologist at Emory University.

Turakhia is a consultant for Precision Health Economics, Medtronic Inc., and St. Jude Medical Inc.

The project was supported by grants from Veterans Affairs Health Services Research and Development Office and the American Heart Association. Stanford’s Department of Medicine also supported the work.
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talking to," said Chang. "Cis’s new tech- nique allowed us to discover the RNA- and protein complexes responsible for X chromosome silencing. The genes for orange and black fur are on the X chromosome in cats. Therefore, a female cat can have a patchwork of both orange and black fur depending on which chromosome was randomly in- activated in each ancestor cell. A male, however, can be orange or black but not both. An exception would be a male cat that had somehow inherited an extra X chromosome along the way, making it an XX cat. XX males are likely to have other signifi- cant genetic problems.)
"Chis’s technique, which the research- ers call CHIRP-MS, "lets us map out identification of RNA-binding proteins by mass spectrometry," allowed the re- searchers to identify the sequential in- teraction of over 80 proteins with Xist during X inactivation. Many of these proteins have never before been associ- ated with that process or thought that they might help target and anchor Xist to active genes along the length of the X chromosome like burrs on a shoelace ac- tivating the X chromosome in a sequential fashion. Specifically, the researchers suspect that some proteins help Xist locate and silence active genes, while others work to maintain that silencing once it has been active genes and shut- ting them down. It also must stay anchored to the chromosome and not float over to any other chro- mosomes in the nucleus. This re- quires an elabo- rate set of machinery that we believe acts in a sequential fashion.
"We’re interested in really understand- ing these concepts, such as vari- ations in expressing patterns among phosphins, randomization and information conveyed concerning patients’ preferences for being notified about studies, and their perceptions of risk and willingness to participate in research. The three scenarios were presented in videos, which are available at http:// spectrum.stanford.edu/romp-videos. During the process of developing and testing the videos and survey, the bio- ethicists learned a great deal about the best way to educate patients on medi- cal research, Magnus said. "One of our first challenges was to dispel the ‘doctors know best’ myth. Doctors don’t always know which treatments are best for indi- vidual patients," he said. "In the absence of good evidence, these choices are often influenced by advertising, insurance cov- erage and local preferences. But this myth was essential in explaining why comparative-effectiveness research is so important."
Hearing it from their doctors
One interesting survey finding was that patients preferred that their doc- tors, rather than medical researchers, ask them whether they’d like to participate in research. This runs counter to conven- tional wisdom in the research commu- nity, where the participation of doctors in the recruiting process can be viewed as a potential conflict of interest. For supporters of comparative re- search in clinical settings, it was encour- ageing to learn that 97 percent of the respondents agreed that health systems should conduct this type of research. "I think that patients really want us to make it easier for them to participate in research," said Magnus. "At medical re- search evolves, the ways that we engage and inform patients must evolve, too." Some of the ROMP team members were recently awarded a grant from the National Institutes of Health to continue researching the ethics of informed con- sent. Next, they will be translating their educational videos into Spanish and Mandarin, and developing strategies and tools for educating patients from diverse ethnic groups about research that makes use of electronic medical records and stored biological samples.
The project is supported by the NIH National Center for Advancing Transla- tional Sciences’ Clinical and Transla- tional Sciences Award to the Institute of Translational Health Sciences at the Uni- versity of Washington and to Spectrum, the Stanford Center for Clinical and Translational Research and Education. The Office of Human Research Pro- tections guidance on patient disclosure over the course of clinical research con- ohr/newsroom/rfc/draftstandarde- search.html.
Kris Newby is the communications man- ager for Spectrum, the Stanford Center for Clinical and Translational Research and Education.

Registration open for Health Matters, a community event
A community event that explores the latest in advancements in medi- cine and health at Stanford Medicine will take place from 9 a.m. to 2 p.m. May 16 at the Li Ka Shing Center for Learning and Knowledge. The event, Health Matters, is free and open to the public. It will feature educational programs about health for the entire family, including lec- tures by Stanford Medicine faculty members on maintaining cognitive health and preventing dementia, preventing heart disease, reducing the risk of infectious disease, under- standing breast cancer biology, and staying healthy and injury-free while exercising, as well as one on genetics research on longevity and aging.
"One thing we truly appreciate on the Stanford campus is having col- leagues a few steps away who work different disciplines," said Lloyd Minor, MD, dean of the Stanford University School of Medicine. "The opportunity to collaborate with so many top experts in an array of fields enriches your own work and accelerates the speed at which new knowledge about how disease works can be transformed into better, safer treatments. Likewise, collaborating with our local community deeply matters."
In celebration of the 25th anniver- sary of the Stanford Health Library, medical librarians will be on hand to answer health questions and help visitors research health-related topics. High school students can take part in a "mini medical school" program. Event-goers can also visit the health pavilion, a collection of exhib- its featuring interactive, hands-on at- tractions and activities for the whole family: Climb aboard the Stanford LifeFlight helicopter; play with cut- ting-edge robotic and 3-D technolo- gies; cuddle up with canines from the pet-assisted wellness (PAW) pro- gram; get answers to health questions from a variety of Stanford experts; and watch cooking demonstrations with Stanford nutrition experts.
Seating at the talks is limited and pre-registration is strongly suggested. The online registration deadline is 5 p.m. May 11. After that time, you can register for the event onsite. For more information and to reg- ister online, visit http://healthmat- ters.stanford.edu.
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Hidden patterns within this spontaneous neural noise, particularly if one might provide a window into the organization of the brain. Dozens of networks — distributed clusters of brain regions dedicated to various mental activities — are continually under consideration. Those patterns that persist across a number of different recordings in individuals who have undergone an invasive procedure for medical purposes. The subjects involved in the "Neuro" study were patients with epilepsy who were in the process of being evaluated at Stanford Hospital for about a week, during which time their brains were monitored in an effort to detect the electrophysiology, providing resolution at a scale of milliseconds and millimeters, letting researchers obtain meaningful results from inspecting a single individual's brain.

Sparing on the brain

Intracranial electrophysiology's precision comes from making high-density recordings in individuals who are a tight-skinned species, and scarring served that prior to the third trimester of pregnancy, human fetuses heal with -

Role of cell type in scarring

The researchers also found evidence pointing to a major role for EPF cells in scarring. After diphtheria toxin was applied to wounds on the backs of mice, the wounds healed with less scarring. The EPF cells are clearly responsible for the vast majority of scarring, said Longaker. Complete healing in the diphtheria toxin-treated wounds required an additional six days compared to controls, but much less time was needed to achieve a scar that appeared to function normally. In contrast, scarred skin is frequently less flexible and weaker than uninjured skin.

When the researchers analyzed the EPF cells more closely, they found that these cells had a different surface. CD26 is highly implicated in the metastasis of many melanomas, but the diphtheria toxin had no effect on epithelial melanoma cells. Instead, it shut down. Previously, Parvizi and colleagues were able to spy, simultaneously, on the tissue within two key nodes of a very important network -

Funding walk to focus awareness on suicide prevention

A Stanford campus walk to focus awareness on suicide prevention will take place on campus next week, with check-in time at 8:30 a.m. The event, a fundraiser for the American Foundation for Suicide Prevention, is organized by the Omicron Chi chapter of Delta Sigma Theta sorority and sponsored by the Department of Psychiatry and Behavioral Sciences.

To register for the Out of the Darkness walk at Stanford, visit http://adp. donordrive.com/event/stanford.82
By Bruce Goldman

Karl Deisseroth, MD, PhD, will receive the Albany Medical Center Prize in Medicine and Biomedical Research for his pioneering work in optogenetics.

Deisseroth is a professor of bioengineering and of psychiatry and behavioral sciences at Stanford University. He also holds the D.H. Chen Professorship. He will share the $500,000 prize with Sunny Xie, PhD, a professor of chemistry and chemical biology at Harvard, who is a pioneer of single-molecule biophysics, chemistry and its application to biology.

The two will be presented with the prize at a ceremony and press conference in Albany, New York, on May 15.

“Dr. Deisseroth’s groundbreaking work in optogenetics presents enormous potential in this young and emerging field,” said Lloyd Minor, MD, dean of the School of Medicine. “Optogenetics offers great hope for patients suffering from neurological conditions to improve human health. We congratulate Dr. Deisseroth on this important and deserved honor. Research in this field is critical to understanding the biology of health and disease.”

Developed over the last 10 years, optogenetics mixes optics, genetic engineering and several other disciplines. It uses photosensitive proteins to control or activate the firing of neurons in animals or brain slices.

Deisseroth pioneered optogenetics, a technology that uses light and genetically altered microbial proteins to activate or inhibit the firing of neurons in animals. By precisely controlling the light-sensing proteins, scientists can then observe the effects of these manipulations on animals’ behavior and deduce the role played by particular nerve cells, relays and circuits.

Medical students awarded 2015 Soros Fellowships

Three Stanford medical students are among the 30 recipients of the 2015 Paul and Daisy Soros Fellowships for New Americans, which support graduate studies for immigrants to the United States and their children.

Each of the Soros Fellows, selected from a pool of 1,200 applicants, can receive as much as $90,000 for tuition and living expenses in support of graduate education.

Cecil Benitez, MD, a medical student, was born in Mexico and moved to the United States with her family when she was 9 years old. She earned a PhD in development biology at Stanford, studying the transcriptional networks of the development of insulin-producing cells in the pancreas. Her work led to numerous publications, including a chapter in a biology textbook.

Paras Minhas, MD, is a student in the MD/PhD program and is working toward a PhD in neuroscience. He is the son of Sikh immigrants and grew up in Maryland. He attended the University of Pennsylvania, where he conducted research on Parkinson’s and Alzheimer’s diseases, which led to several scientific publications. He recently co-managed Stanford’s Pacific Free Clinic in east San Jose. He currently works in the laboratory of Katrin Andreasson, MD, studying the inflammation and bioenergetics of neurodegenerative disorders.

Gerald Chunt-Sein Tiu is a student in the MD/PhD program and is working toward a PhD in genetics. He is the son of Burmese-Chinese parents who emigrated to California from Myanmar. He graduated summa cum laude in chemical and physical biology from Harvard University. Then, he was awarded a Michael C. Rockefeller Fellowship to study the social, political and cultural dynamics of HIV in China and Myanmar. He works in the laboratory of Maria Barna, PhD, on RNA-mediated gene regulation in mammalian development.

Detecting lymphoma relapse by monitoring cell-free tumor DNA

By Krista Conger

Circulating tumor DNA in the blood of patients treated for non-Hodgkin lymphoma can be used to identify those who are relapsing earlier, and with greater accuracy, than conventional monitoring, according to a study by researchers at the School of Medicine.

The finding is important because it will allow clinicians to quickly identify patients who need additional treatment. It also further validates the use of circulating tumor DNA as a means to detect or monitor cancers.

“Diffuse large B-cell lymphoma is the most common blood cancer,” said Ash Alizadeh, MD, PhD, an assistant professor of medicine and a member of Stanford’s Cancer Institute. “This disease is curable in most patients, but a significant minority of these patients will relapse. Right now, we don’t have a good way to identify those who fall into this category.”

The current standard for detecting the cancer in these patients is imaging with combined PET and CT scans. However, imaging is limited by its specificity: not every positive PET scan means a patient has truly relapsed.

A paper describing the new research was published last month in Blood. Alizadeh is the senior author, and doctoral scholar David Kurtz, MD, and former postdoctoral scholar Michael Green, PhD, share lead authorship. The research team used a high-throughput sequencing technique to look for the sequence in the patient’s blood, both in the plasma (the straw-colored, cell-free liquid in which blood and immune cells circulate), and in the patient’s circulating immune cells.

The researchers found that, in patients known to be relapsing, they could reliably detect the tumor DNA in the plasma. In contrast, when they examined the circulating cells in the blood they could detect the disease in only 30 percent of the relapsing patients. They then compared their plasma-based method with PET/CT scans. Studying patients who would go on to relapse, they found their new method identified all patients at the time of their relapse, and often was able to detect disease prior to relapse. Furthermore, the test was positive only in those patients who truly had relapsed. In contrast, a positive PET/CT scan was correct only 56 percent of the time.

Alizadeh cautions that it’s not yet possible to identify the unique cancer-specific DNA sequence in every patient. About 10 to 30 percent don’t have enough circulating tumor DNA to do so. “This is all about sharpening the tool,” Alizadeh said, “but the specificity of this new approach is very promising.

Other Stanford co-authors are postdoctoral scholars Scott Bramtan, MD, PhD, and Florian Scherer, MD; research associate Chu Long Liu, PhD; research fellow Christian Kunder, MD, PhD, former postdoctoral scholar Kazuhiro Takahashi, MD, PhD; clinical trials assistant Cynthia Glover; research assistant Shingo Kihira; assistant surgeon Brendan Visser, MD, data manager Karen Corbelli; assistant professor of medicine David Miklos, MD, PhD; professor of medicine Ranjana Advani, MD; founder of medicine Ronald Levy, MD; and assistant professor of radiation oncology Maximilian Diehn, MD, PhD. The research was supported by the Stanford Cancer Institute Innovation Fund Award, the Stanley Hack Family Foundation, the Evelyn Leung Memorial Foundation and the Lymphoma Research Foundation.

Stanford’s Department of Medicine also supported the work.