To keep players off the sidelines, Dragoo stresses injury prevention

By Elizabeth Devitt

It’s said that experience is the best teacher. In the case of Jason Dragoo, MD, an orthopaedic surgeon at Stanford who specializes in knee injuries, experience may also make the best healer. During his college football career as a defensive safety, Dragoo endured many injuries. In the end, he spent as much time in doctors’ offices as he did on the playing field. “It really helps for sports medicine physicians to have experienced injuries themselves,” he said. “I understand how long it takes each of these athletes to get where they are, whether it’s an NCAA competitor, an Olympic hopeful or a professional athlete. It takes years of commitment and effort to get to their skill level, so if I can help them achieve their goals without injury, it’s very satisfying to me.”

Dragoo joined the faculty in 2005 and is an associate professor in the Department of Orthopaedic Surgery. He divides his time between clinical work, the surgery suite, stem cell research, the Human Performance Lab and the care of Stanford athletes. He also has served as head physician of Stanford’s football program for the past six years. He credits the injury prevention programs developed by Stanford Sports Medicine and strength and conditioning specialists at Stanford with keeping elite athletes playing on all the university’s sports teams. For 18 consecutive years, Stanford University has won the Division I Learfield Sports Directors’ Cup, given annually to the best overall intercollegiate athletic program in the country. The football program’s recent rise from middle of the Pac-12 to national powerhouse has also contributed to Stanford’s ongoing success.

“Earning those accolades takes talented athletes and great coaches. But you can’t win if you can’t keep your players in the game,” Dragoo said. “Maintaining injury-free athletes isn’t easy. For example, a whopping

Blood transfusions dip at Stanford, scientist says

By Ruthann Richter

After steadily increasing over two decades, blood collections and transfusions nationwide are on the decline, with Stanford University Medical Center among a number of institutions that have taken steps to effectively reduce the use of precious blood supplies, according to a newly published study.

Though the nation’s blood supply has never been safer, blood transfusion has always been recognized as carrying risks, including possible outcomes related to longer hospital stays, immune system changes leading to cancer recurrence, multi-system organ failure and exposure to unknown, emerging pathogens, said Lawrence Goodnough, MD, professor of pathology and of hematology at the School of Medicine.

“We think blood saves lives, though that has never been proven,” said Goodnough, who is also director of the transfusion service at Stanford Hospital & Clinics. “So it’s a matter of less is more. There is such a thing as over-transfusion, and I think people are increasingly recognizing that.”

He has written a commentary and co-authored two papers in a clinical series on transfusion medicine published in the May 25 issue of Transfusion, page 4

Study: Brain makes own version of Valium

By Bruce Goldman

Researchers at the School of Medicine have found that a naturally occurring protein secreted only in discrete areas of the mammalian brain may act as a Valium-like brake on certain types of epileptic seizures.

The protein is known as diazepam binding inhibitor, or DBI. It calms the rhythms of a key brain circuit and so could prove valuable in developing novel, less side-effect-prone therapies not only for epilepsy but possibly for anxiety and sleep disorders, too. The researchers’ discoveries were published May 30 in Neuron.

“This is one of the most exciting findings we have had in many years,” said John Huguenard, PhD, professor of neurology and neurological sciences and the study’s senior author. “Our results show for the first time that a nucleus deep in the middle of the brain generates a small protein product, or peptide, that acts just like benzodiazepines.” This drug class includes not only the anti-anxiety compound Valium (generic name diazepam), first marketed in 1965, but its predecessor Librium, discovered in 1955, and the more recently developed sleep aid Halecyon.

Valium, which is notoriously addictive, prone to abuse and dangerous at high doses, was an early drug treatment for epilepsy, but it has fallen out of use for this purpose because its efficacy quickly wears off and because newer, better anti-epileptic drugs have come along. For decades, DBI has also been known to researchers under a different name: ACBP. In fact, it is found in every cell of the body, where it is an intracellular peptide, that acts just like benzodiazepines. This drug class includes not only the anti-anxiety compound Valium (generic name diazepam), first marketed in 1965, but its predecessor Librium, discovered in 1955, and the more recently developed sleep aid Halecyon.

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Ethnic background plays a surprisingly large role in how diabetes develops on a cellular level, according to two new studies led by researchers at the School of Medicine. The researchers reanalyzed disease data to demonstrate that the physiological pathways to diabetes vary between Africa and East Asia and that those differences are reflected in part by genetic differences. The studies were published online simultaneously May 23 in the journals PLoS Genetics and Diabetes Care.

“We have new insights into the differences in diabetes across the world, just by this new perspective applied to older data,” said Anil Butte, MD, PhD, professor and director of the studies and chief of the Division of Systems Medicine and associate professor of pediatrics and of genetics. “There’s more to learn about diabetes than we knew.”

The early stages of type-2 diabetes, or adult-onset diabetes, can develop when the pancreas has problems creating sufficient insulin, a hormone crucial for regulating blood sugar, or when the body’s cells have trouble responding to insulin, a condition called “insulin resistance.” Both problems will lead to the same result: too much sugar in a person’s bloodstream, which is the main criterion for diagnosing diabetes. Diabetes develops by low insulin secretion and insulin resistance as the disease progresses.

In the study published in PLoS Genetics, the researchers started by studying genome information of more than 1,000 people in 51 populations from around the world. These individuals were from indigenous populations, representing the earliest groups of humans at various locations. Lead author and former graduate student in Butte’s lab, Erik Corona, PhD, studied more than 100 diseases searching for genetic differences in risk across these native populations, and found a clear genetic pattern for type-2 diabetes. The genetic risk is highest for Africans and drops along the trajectory the first humans took when migrating out of Africa toward East Asia (primarily Japan, China and Korea), where diabetes-linked genes appear to be more protective. Based solely on what is currently known about type-2 diabetes genetics, native Africans would appear to be at higher risk for diabetes, while East Asians would appear to be protected. But East Asians are not necessarily at lower risk of diabetes than Africans. Butte pointed out that “East Asians definitely get diabetes. What we would argue is that diabetes may be a different disease” in East Asian populations. An interactive tool that displays the results can be found at http://geneworld.stanford.edu.

The genetics study’s findings led Butte’s team to wonder if there was clinical evidence of these differences in African and East Asian populations. For the second paper, lead author and staff engineer research associate Keichi Kodama, MD, PhD, pulled data from more than 70 papers looking at simultaneously measured insulin secretion and insulin resistance in individuals across three different ethnic groups: Africans, Caucasians and East Asians. They found that at baseline, Africans had higher insulin resistance but were able to compensate with higher insulin secretion. East Asians were more likely to have less insulin-secretion ability, but this was compensated by having normal insulin resistance. Caucasians fell between these two groups, though they were more likely to develop problems with insulin secretion.

The researchers noted that because individuals from each ethnic group start at a different baseline position, they each reach diabetes in a different way: Africans through increased insulin resistance, and East Asians through lower insulin-secretion ability. “Africans are already pretty insulin resistant,” Butte said. “They need their beta cells to work really hard. If their cells fail, that’s how they head toward diabetes. East Asians, in contrast, ‘don’t have a lot of spare capacity to secrete more insulin.’ The findings were published in Diabetes Care. Butte notes that a shift in how clinicians think about diabetes could lead to more targeted therapies, much as how thinking about cancer has evolved over the past 10 years, leading to new treatments. “Other fields of medicine have undergone a radical rethinking in disease taxonomy, but this has not happened yet for diabetes, one of the world’s public health menaces,” he said. “If these are separate diseases at a molecular level, we need to try to understand that.”

Other Stanford co-authors include past bioinformatics scientist Rong Chen, PhD; Carlos Bustamante, PhD, professor of genetics and co-director of the new Stanford Center for Computational, Evolutionary and Human Genomics; former graduate students Alexander Morgan, PhD, and Aditya Ramesh, MS; and postdoctoral scholars Chirag Patel, PhD, and Martin Sikora, PhD. Scientists at Lund University in Malmo, Sweden, also involved in this work.

These studies were supported by grants from the Howard Hughes Medical Institute, the National Library of Medicine and the Lucile Packard Foundation for Children’s Health. The Department of Pediatrics also supported the research. 

Rina Shaikh-Leask is a science-writing intern for the medical school’s Office of Communication & Public Affairs.

Study: Diabetes’ underpinnings can depend on ethnic background

By Rina Shaikh-Leask

Free online ‘Statistics in Medicine’ course starts June 11

By Kris Newby

The School of Medicine will launch its third free online course, “Statistics in Medicine,” on June 11. The nine-week massive open online course — or MOOC, for short — will aim to provide students with a foundation in understanding of probability and statistics, teaching them the skills required to critically evaluate statistics in medical studies. It also will show them how to use these skills to avoid common statistical pitfalls with their own research data.

The course will be taught by Kristin Sainani, PhD, a clinical assistant professor of health research and policy and a recipient of several teaching awards from Stanford’s graduate program in epidemiology. Sainani’s first MOOC, “Writing in the Sciences,” was launched September 2012. More than 43,000 people registered during the initial eight-week course, with 3,547 earning completion certificates. An additional 23,000 students have since registered for the self-paced version of the course, which may be taken at any time, minus peer-reviews and the time for discussions and activities that reinforce the newly acquired knowledge.

Although Sainani’s videolocated lectures were designed for use with the Stanford course, “HRP 258: Introduction to Probability and Statistics for Clinical Research,” the school faculty made the decision to release this foundational course as a MOOC, available worldwide and at no cost.

“Sainani is a very skilled teacher, and the content of her course is relevant to a broad range of learners both within and outside of medicine,” said David Prober, MD, senior associate dean for medical education at the School of Medicine. “Her material will be potentially useful for learners along the continuum, from high-school students to practicing health-care workers. On campus, the broad audience for this class includes undergraduate students, medical students, residents and fellows. The online population of learners could be much more diverse, supporting Stanford’s educational mission to educate as broadly as possible.”

Prober, who oversees the school’s educational programs, explained the importance of embracing this instructional model in a May 2012 New England Journal of Medicine perspective piece, “Lecture halls without lectures: A proposal for medical education.”

The School of Medicine’s fourth MOOC, “Introduction to Statistical Learning,” launched in December 2012 as a resource for the Biostatistics Division. Ultimately, the school’s MOOCs will be made available worldwide, in an online library of teaching modules, under the stewardship of the Stanford Center for Clinical and Translational Education and Research, that can be used by other research institutions.

To learn more about “Statistics in Medicine” and to register for this free online course, go to http://med.stanford.edu/courses/Medicine/HRP258/Statistics_in_Medicine/about.html. The course will be enrolled in the on-campus course, which also includes in-person meet-ups.

Kris Newby is the communications manager for Spectrum, the Stanford Center for Clinical and Translational Education and Research.

"Statistics in Medicine" will use real-world examples from medical literature and popular media to reinforce its lessons. Each week’s opening lecture will begin with a statistical brain teaser: Should you be worried about lead in lipstick? Should you play the lottery when the jackpot reach half a billion dollars? Does eating red meat increase your risk of being in a traffic accident? Sainani will guide students through data as they are presented in the popular press and in the original studies. In the process, students will learn how to read, interpret and critically evaluate statistics in medical studies.

Produced by the Stanford Medicine Interactive Learning initiatives program, the course is part of the medical school’s effort to reimagine and improve medical education through the “flipped-classroom model.” In a flipped classroom, students watch videolocated lectures as homework before class, then use in-class time for discussions and activities that reinforce the newly acquired knowledge. Although Sainani’s videolocated lectures were designed for use with the Stanford course, “HRP 258: Introduction to Probability and Statistics for Clinical Research,” the school faculty made the decision to release this foundational course as a MOOC, available worldwide and at no cost.

Sainani will teach “Statistics in Medicine.” This screen shot is from a video about the free online course, which will aim to give students a foundational understanding of probability and statistics, teaching them the skills required to critically evaluate statistics in medical studies.

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

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Study identifies genetic suspects in Lou Gehrig’s disease

By Krista Conger

Researchers at the School of Medicine have identified mutations in several genes that may be associated with the development of sporadically occurring cases of the neurodegenerative disease known as amyotrophic lateral sclerosis, or ALS.

Ahn also known as Lou Gehrig’s disease, the progressive, fatal condition, in which the motor neurons that control movement and breathing gradually cease to function, has no cure.

A growing number of researchers know of some mutations associated with inherited forms of ALS, the majority of patients have no known genetic cause. And although there are few clues as to its cause. The Stanford researchers compared the DNA sequences of 47 patients who have the spontaneous form of the disease, known as sporadic ALS, with those of their unaffected parents.

The goal was to identify new mutations that were present in the patient but not in either parent that may have contributed to disease development. 

Mutations in genes that encode chromatin regulators — cellular proteins that govern how DNA is packed into the nucleus of a cell and how it is accessed when genes are expressed. Protein members of one of these chromatin-regulatory complexes have now been confirmed to contribute to normal development and some forms of cancer.

Until now, we more about the genetic causes of the disorder, the greater insight we will have as to possible therapeutic targets,” said Aaron Gitler, PhD, associate professor of genetics. “Until now, we have less than 1 percent of the total amount of DNA in each human cell, vastly reduced the number of potential genes involved in these cases are unknown.”

Gitler is the senior author of the study, which was published online May 25 in Nature Neuroscience. Postdoctoral scholar Alessandra Chesi, PhD, is the lead author. They collaborated with researchers from Emory University and Johns Hopkins University to collect these samples.

The researchers compared the sequences of a portion of the genome called the exome, which directly contributes to the amino acid sequences of all the proteins in a cell. (Many genes contain intervening, non-protein-coding regions of DNA called introns that are removed prior to protein production.) Mutations found only in the patient’s exome, but not in that of his or her parents, were viewed as potential disease-associated candidates — particularly if they affected the composition or structure of the resulting protein made from that gene.

Focusing on just the exome, which is about 1 percent of the total amount of DNA in each human cell, vastly reduced the number of potential genes involved in these cases are unknown.”

Gitler and Chesi combined deductive reasoning with recent advances in sequencing technology to conduct the work, which relied on the availability of genetic samples from not only ALS patients, but also the patients’ unaffected parents. Such trios can be difficult to obtain for diseases like sporadic ALS that strike well into adulthood when a patient’s parents may no longer be alive. Gitler and Chesi collaborated with researchers from Emory University and Johns Hopkins University to collect these samples. For the past decade, the university has cued the medical school’s faculty and scholarship that advances clinical medicine. Faculty numbers in the university- tenure line, whose members largely focus on basic science, will likely grow at a more moderate rate than those in the medical-center line, given the limited availability of so-called “wet laboratories” labs equipped to handle experiments with chemicals and biological materials, which are the stock in trade of basic scientists — Jackler said. Faculty in the medical-center line also are key to the school’s goal of augmenting clinical and translational research efforts, he added.

Expanded research opportunities

As part of the school’s push to promote clinical research, clinician- educators can now request principal investigator status on a range of clinical studies. Previously, clinician-educators could only request PI status on multicenter, industry-sponsored clinical trials for which they served as site director. Now, those at the rank of clinical assistant professor and above may request waivers so they can lead trials that include participants at Stanford Hospital & Clinics, Packard Children’s, the Veterans Affairs Palo Alto Health Care System, Santa Clara Valley Medical Center and Stanford-affiliated medical centers. They may also request PI status on a broad spectrum of clinical research, which may involve diagnosis, treatment or rehabilitation of human disease, and lead studies in population science, innovative systems of care, optimization of health-care-delivery models, novel methods of clinical teaching and other forms of clinical investigation.

The changes are partly intended as a show of support for clinician-educators, who, according to the task-force report, sometimes felt undervalued because of the previous limits on their eligibility to conduct research within the medical center.

The situation where clinician-educators were basically excluded from much clinical research, even when we knew that we had superb people interested in doing it, was not ideal when you want these colleagues to feel like they are part of the medical community,” said Harry Greenberg, MD, senior associate dean for research and professor of medicine and pathology. “This is really a big step forward.”

More information about the changes and instructions about requesting PI waivers, visit the school’s Research Management Group website: http://med.stanford.edu/rgm. html

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one in 10 college-age females will dam-
gerous injuries. His results are published
in numerous peer-reviewed journals, in-

“We’ve identified a hormone in some women that appears to make them more at risk,” Dragoo said. “That hormone, called relaxin, dissolves knee ligaments. A ligament-loosening agent can be a good thing during childbirth when the pelvis needs to widen to accommodate a baby. It’s not so great when there’s no baby on the way and other important ligaments are weakened.”

Dragoo’s research confirmed the pres-
ence of relaxin receptors on the anterior cruciate ligament and showed that relaxin activated those receptors. It also has shown that intercollegiate female athletes with ACL tears had higher levels of relaxin in their blood, which appeared to increase their risk for ligament rupture.

“We also know the concentration of relaxin in the blood that puts women at risk,” Dragoo said. The next step will be creating a blood test that accurately identifies at-risk female athletes, as well as developing a safe and effective medi-
cation to counteract the effects of the hormone on the knee ligaments while women are pursuing athletics.

Currently, Stanford athletes are learn-
ing to protect themselves from injury through physical training programs that teach proper body mechanics. Dragoo found most existing programs were too easy for elite sports competitors. “So we created the Elite Athlete ACL Prevention program where we push athletes to the edge of being in control,” he said. “We create unstable surfaces — such as soaking wet playing fields or basketball courts made slippery by wearing socks — and ask them to perform specific maneuvers. If they aren’t in the mechanically-appropriate position to do so, their feet will slide out from under them.”

With continued training, the athletes learn safer biomechanical movement patterns that, ideally, become second nature during competition.

The elite program started in 2011 for several Stanford sports teams. This year, the women’s soccer team is participating. “Although it’s early in the implementation period, there has already been a marked decrease in knee ligament inju-
ries,” Dragoo said.

The third approach in the Stanford Sports Medicine injury prevention plan is SmartBrace technology. “It’s an entirely different strategy compared to cur-
ting knee braces,” Dragoo said. Traditional braces don’t prevent many injuries because they can’t effectively stabilize the knee joint in all directions. So, with the advent of intensive screening and an understanding of knee injuries, Dragoo and his team created a new brace in collaboration with a prosthetics braking specialist and Stanford’s departments of electrical and mechanical engineering.

The SmartBrace senses an athlete’s movement and provides instant informa-
tion through built-in computerized feedback devices. “There are certain movement patterns that can make them more susceptible to ligament tears,” Dragoo said. The brace identifies these patterns and gives “haptic feedback” — it vibrates in response to the wrong type of motion. If the wrong movement pattern is re-
peated, the brace sensors buzz again. So an athlete gets constant, real-time rein-
forcement to retrain themselves to move correctly. “I really believe this brace is going to change the ballgame,” he said.

The next step is to test the beta ver-

tion of the brace. “We need to make sure the brace accurately assesses movement — that it will identify at-risk move-

tments and lead to a change in the ath-


elete’s body mechanics,” Dragoo said. Athletes outside Stanford also ben-
efiting from Dragoo’s expertise. He’s a team physician for the U.S. Olympic Com-


tee and the U.S. Ski Team.

Despite running a schedule that would
make an endurance athlete weary, Dragoo
makes certain he saves time to spend with his family. “That’s the most precious time for me,” he said. Fortunately, his family also loves Stanford sports. Dragoo said his 4-year-old and 7-year-old have never missed a home football game. “They know all the players by name,” he said. “It’s a good way for them to grow up. They see football as a fun and college as a normal part of their future.”

Elizabeth Devitt is a former science-writ-
ing intern for the medical school’s Office of Communication & Public Affairs.

Transfusion continued from page 1

of the Lancet, the series focuses on trends in blood in-

dustry, blood transfusion and alternatives to blood.

Stanford medical center is among the institutions
that have made a concerted effort in recent years to de-
crease the use of blood supplies. In 2009, a multidis-
ciplinary force at the center spearheaded an effort to capi-
talize on the electronic medical records system at Stanford Hospital & Clinics to encourage doctors to think twice before ordering transfusions. Now, if a physician tries to order blood for a patient with levels of hemoglobin — the quantity of red blood cells carrying oxygen in the body — above a certain level, a pop-up on the screen alerts the doctor to guidelines on when to transfuse blood and asks the clinician to explain the reason for the request. This appears to cause some phy-

sicians to reconsider or cancel the order for blood trans-
fusion, Goodnough said.

The result is that use of red blood cells at the hospital fell from 30,443 units in 2009 to 23,118 in 2012 — a 24 percent decrease. Transfusions of all blood products at the hospital declined from 60,204 to 48,678 during that same period.

“We are leveraging elec-

tronic medical records to reverse this national trend toward over-

utilization and encourage people to follow a more restrictive blood practice,” Goodnough said.

“We’re very proud of what we’re doing here at Stanford.”

Goodnough, who has devoted much of his career to blood conservation, notes that the use of blood briefly declined in the early 1980s in response to the AIDS epidemic, as well as to the wide-

spread problem of hepatitis C infection among trans-

fusion patients undergoing heart surgery. However, with the advent of intensive screening and other safety measures, the number of transfusions began steadily rising, largely because of the demands of specialized care and aging population, he said. Today, some 24 million blood components, including red blood cells, plasma and platelets, are transfused annually in the United States.

Among the 39 million pa-

tients discharged annually from U.S. hospitals, 2.5 million — or 5.8 percent — received transfu-
sions, according to the report.

The downward trend in blood usage began in 2009, largely in re-


to the rising costs of blood, which can run between $500 and

$1,000 for each transfused unit, Goodnough said. For the first time, transfusions of blood com-

ponents provided by the American Red Cross, which collects about a third of the blood it distributes, fell from 30,443 units in 2009 to 23,118 in 2012 — a

24 percent decrease. Transfusions of all blood products at the hospital declined from 60,204 to 48,678 during that same period.

There is such a thing as over-transfusion, and I think people are increasingly recognizing that.”

Despite growing evidence about the dangers of un-

necessary transfusions, he said there continues to be a wide variation in practices across the country, suggesting blood is often used inappropriately, said Lawrence Goodnough.

“ ‘If you look, for instance, at patients undergoing coronary artery bypass surgery, there is widespread variability throughout the United States for a routine bypass or valve replacement on transfusion outcomes, with regional differences and differences among aca-

demic and community medical centers,” he said.

He said the American Medical Association has high-

lighted the danger of unnecessary transfusion and in-
cluded blood transfusion among a list of five overused


treatments. (The others were heart stents, ear tubes, an-


tibiotics and the induction of birth in pregnant women.)

Yet changing clinical practice to ensure that every

patient can do just as well with

other treatments. (The others were heart stents, ear tubes, an-


tibiotics and the induction of birth in pregnant women.)

"I don’t think there is one laboratory value that should be used. Older patients may be different than younger patients, for instance,” he said. “So the mes-
sage is that there is not one number. We should use a restrictive transfusion philosophy — when the treating team is convinced that the benefits of transfusion would outweigh the risks.”

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necessary transfusions, he said there continues to be a wide variation in practices across the country, suggesting blood is often used inappropriately, said Lawrence Goodnough.
Scientists consider the potential of abundant biomedical data

By Bruce Goldman

A “tsunami of digital data” now surges through medical research and health care, Lloyd Minor, MD, dean of the School of Medicine, told a packed auditorium May 22 at the start of the Big Data in Biomedicine Conference at Stanford.

The ease with which patient electronic records, DNA-sequencing data, comprehensive biological data on disease mechanisms, treatment monitoring reports, clinical trial results, pharmaceutical records, disease registries, and so on can be transmitted, the goal of a mini symposium earlier this week, said May 22-24 in the Li Ka Shing Center for Learning and Knowledge, was to harness the power of that data. The conference was presented by Stanford Medicine and the University of Oxford, and sponsored by the Li Ka Shing Foundation.

The data can be understood as “a challenge so big and so complex that single individuals or companies or institutions cannot solve it alone,” it would, he said, require a collaboration between academia, philanthropy, industry and government.

More than 40 speakers from across the United States and several foreign countries brainstormed to improve health care by using “big data.” “If cars had made as much progress as computers over the past several decades, you’d be able to drive across the country for a dime in one of them and then pack it up and stick in your shirt pocket,” Stanford University President John Hennessey, PhD, a computer scientist, told the audience of roughly 300 people in the Li Ka Shing Center’s Berg Auditorium. (Another 400 people watched parts of the conference online.)

Vast increases in data-processing capacity have coupled with accelerated data-transmission capability to make possible prospects for improving patients’ compliance, providers’ diagnostic and therapeutic marksmanship and researchers’ ability to tease apart causality from mere correlation. “The amount of data being generated worldwide each year now falls in the zettabyte range,” said Avul Butte, MD, PhD, chief of systems medicine and associate professor of pediatrics and of genetics, and the conference’s principal organizer. The prefix “zetta-” refers to the number 1 followed by 21 zeroes.

This data includes studies of substances and gene activity in healthy and diseased blood and tissue samples, as well as analyses showing the effects of drugs on such samples. Butte described one set of studies conducted in his lab as “a kind of Match.com for medical molecules.” Exploiting publicly available databases, his team found several instances in which a drug’s effects on gene activity in a particular tissue was the opposite of the changes in gene activity wrought by a specific disease. Never mind that this drug had never even been previously considered as a therapy for that disease. Pairing the drug and disease off produced promising therapeutic results. Moreover, the candidate drug was off-patent — therefore potentially cheap — and well-studied — therefore known to be safe — accelerating their potential progress through the development mill.

As many as 1.2 million “gene-expression analyses,” in which each gene in the genome is assessed by a high-tech, high-speed device such as the 23andme, are already stored on the Internet, Butte said, and that number doubles every two to three years. “Instead of dissecting a frog, any high-school kid today who needs to do a science project can go to a public National Center for Biotechnology Information database, type ‘breast cancer’ in the appropriate field, and pull down 37,000 digital samples of breast cancer as easily as she could find a song on iTunes.

But there may be a way around that. Keynote speaker Anne Wojcicki, co-founder and CEO of the personalized genomics company 23andme, described her business’s success in connecting people with their genetic data, which she said has often been discouraged in the past. Audience members (bottom) packed Berg Hall, in the Li Ka Shing Center for Learning and Knowledge.

Wojcicki said that most genetic variants are rare. Learning about the existence, let alone the significance, of such variants requires large-scale studies, he said, Anne Wojcicki (top right), co-founder and CEO of the personalized genomics company 23andme, spoke at the conference, describing her business’s success in connecting people with their genetic data, which she said has often been discouraged in the past. Learning about the existence, let alone the significance, of such variants requires large-scale studies. “But epidemiological studies of 1 million people are extraordinarily expensive. To do 50 million or 200 million is all the more so.”

But there may be a way around that. Keynote speaker Anne Wojcicki, co-founder and CEO of the personalized genomics company 23andme, described her business’s success in connecting people with their genetic data, which she said has often been discouraged in the past. “Keeping you from accessing your genetic data is like telling you that you can’t look in a mirror,” Wojcicki said. 23andme’s database now numbers 250,000 genotypes, each labeling the results of 1 million separate searches at specific spots on an individual’s DNA for genetic variants. 23andme hopes to have sold 1 million such searches in its database by year end. These individuals’ genomics, in the aggregate, constitute a vast source of data for low-cost, large-scale studies.

People who have been genotyped, Wojcicki said, are remarkably willing to share their personal data if they can be sure that there will be no use of it against them. “Data is useful to medical practitioners and researchers,” Butte said. “We don’t live with our patients. We get to see them only in the hospital or when they come for a visit to our office. How do we track these patients?” How can we keep them compliant?

With patient medical records plus data, environmental samples and more increasingly available, a big challenge will be to integrate those disparate sources. One speaker, John Bell, MD, of Oxford, referred to this challenge as “big data in the wild: not necessarily well-controlled, carefully collected or consistently organized.” Bell highlighted the need to create “data havens,” where data can be stored and retrieved for research purposes under conditions that absolutely ensure patients’ privacy — a precondition for obtaining their buy-in — and to give patients a sense that this research will pay dividends to them in the form of a more efficient health-care system and fewer adverse drug effects, for example.

Another challenge is cost. Carlos Bustamante, PhD, professor of genetics and a conference organizer, explained that most generic variants are rare, occurring in perhaps one of every 3,000 individuals. Learning about willingness to enroll in studies, answer survey questions and even, in some cases, submit to biopsies.

Wojcicki asserted that knowing about your genetic predispositions can change your behavior, potentially also reducing national health care costs. Noting that her husband, Google co-founder Sergei Brin, carries a gene variant predisposing him to increased risk of Parkinson’s disease, Wojcicki said that this has spurred their family to take steps to mitigate the risk via lifestyle changes. “We drink more coffee, which many studies have found to be protective. We exercise all the time.”

Michael Snyder, MD, PhD, professor and chair of genetics, is another beneficiary of detailed research on his genome. He recounted the story of his voluntary submission to an ongoing analysis of the relative activity levels of each of his genes, myriad proteins and other blood-borne substances as part of a scientific experiment to determine the value of such intensive personalized analysis.

“I’ve been getting profiled for more than three years now and had 60 samples taken, followed by the measurement of billions of different molecules,” he said. Revealed in the course of this series of assessments was Snyder’s blood-glucose level’s climb, shortly after a viral infection, into the diabetic range. Catching this medically significant development early on, modifying his diet and boosting his exercise regimen have resulted in the return of Snyder’s blood-glucose levels to the normal range — without any need for ongoing drug therapy, he said.

Euan Ashley, MD, PhD, assistant professor of cardiology, personalized medicine and one of the scientists monitoring Snyder’s molecules, discussed the difficulty inherent in ultra-detailed personalized analysis. “Most people are average in most things,” he said. “What you want to know is where people are not average. ... You’re looking for not needles in haystacks, but needles in stacks of needles.”

With 6 million data points in each person’s genome, accuracy is an imperative. Fortunately, accuracy is increasing as costs are plummeting. Ferraris, Ashley said, are now weighed in with a cost upward of $300,000 each. If that brand’s cost had dropped as much as that of gene sequencing has, you could get one for 40 cents.

Among this conference’s final announcements: the next one, in what is expected to become annual event, is already scheduled to take place in the same building on May 21-23, 2014.
Scientists at the School of Medicine have shown that their previously identified therapeutic approach to fighting seizures, which blocks called macrophages, also prompts the disease-fighting killer T cells to attack the cancer.

The research, published online May 20 in the Proceedings of the National Academy of Sciences, demonstrates that the approach may be a promising strategy for creating custom cancer vaccines.

Various researchers have been working over the years to create vaccines against cancer, but the resulting vaccines have not been highly effective. Developing vaccines that engage the vaccines relying on using immunocytes called dendritic cells to introduce cancer protein or peptide fragments to T cells — a process known as antigen presentation. The hope has been that the process would stimulate the body's T cells to identify cancer cells as diseased or damaged and target them for elimination. However, this process often only modestly activates the most potent cancer-killing type of T cell, called killer T cells or CD8+ T cells.

The Stanford team discovered that there was another catch in the vaccine strategy, when the macrophage pathway to program killer T cells against cancer. Irving Weissman, MD, professor of pathology and of developmental biology, and his team previously showed that near this region; in the corticothalamic circuit, at least, DBI appears to be implicated in the initiation of seizures. But until now, exactly what this benzodiazepine-binding site was defec-
tively, they showed that DBI lost its effect, which Huguenard and Christian suggested makes these mice seizure-prone.

In another seizure-prone mouse strain in which that site is intact but the gene for DBI is missing, the scientists saw diminished inhibitory activity on the part of benzodiazepine-responsive GABA receptors. Re-introducing the DBI gene to the brains of these mice via a sophis-
ticated laboratory technique restored the strength of the GABA-mediated inhibition. In normal animals, compounds that bind to benzodiazepine-binding sites weakened these same receptors' inhibitory activity in the thalamic reticular nucleus, even in the absence of any administered benzodiazepines. This suggested that some naturally occurring benzodiazepine-like receptor-binding protein was binding to the GABA-binding site, the researchers noted. In DBI-deficient mice, the blocking activity on benzodiazepine-binding sites by the drug.

Huguenard's team also showed that DBI has the same inhibition-enhancing effect on nerve cells in an adjacent thalamic region — but also that, importantly, no DBI is naturally generated in these sites. Therefore, DBI may offer new route to successful cancer vaccination, study finds

By Christopher Vaughan

New research on fighting cancer with immune system to wage a two-pronged attack provides hope that the therapy will cause the immune system to differentiate from the cancer. There are two successful cancer vaccines, but until now, the process has been that the process would activate their own immune system to attack cancer and immune response against it. Levy said. "With these negative regulatory cells out of the way, the killer T cells of the immune system are unleashed to seek and destroy the cancer cells wherever they are in the body, including in the brain."

Levy and his colleagues first found evidence in which human lymphoma cells had been implanted under the skin or injected into the blood. Once tumors were established, they

The work, which has resulted in the recent initial phase-1 and -2 clinical trial in humans, was published May 24 in the Journal of Clinical Investigation. "These monoclonal antibodies target and eliminate T regulatory cells mixed in with the tumor that dampen the immune response against it," Levy said. "With these negative regulatory cells out of the way, the killer T cells of the immune system are unleashed to seek and destroy the cancer cells wherever they are in the body, including in the brain."
Engineered molecules boost immune attack on cancer, researchers say

By Christopher Vaughan

Building on previous research showing that cancer cells send signals to the immune system to avoid being attacked, a team of engineers designed molecules that are highly proficient at neutralizing those signals.

The molecules dramatically increase the effectiveness of the immune system by attracting immune cells called macrophages. The scientists found that when they used drugs to block this “don’t eat me” signal, macrophages engulfed and destroyed the cancer cells.

More recently, Stanford scientists wondered if they could engineer molecules that block the signal more effectively. They began by modifying a protein called SIRP-alpha, which is found on macrophages and is the natural receptor for CD47. In a research paper published online May 30 in the journal Science, a team that includes working with School of Medicine professors Christopher Garcia, PhD, and Irving Weissman, MD, report that they have engineered new versions of SIRP-alpha that bind much more strongly to CD47 than the natural version of the molecule, making them extremely potent blockers of the “don’t eat me” signal.

Two MD/PhD students in the Stanford Medical Scientist Training Program — Kipp Weiskopf, MPhil, and Aaron Ring, MS — devised the strategy for engineering the molecules and were lead authors of the Science paper.

“This is the best example of how science and medical training can lead to discovery and medical translation,” Weiskopf said. “Weiskopf and Ring fleshed out the ideas that led to this project, bringing the complementary expertise to make it happen.”

The engineered SIRP-alpha variants bind approximately 50,000 times more strongly to CD47 than natural SIRP-alpha, nearly potently as the most powerful drugs, Weiskopf said. But the researchers found blocking the CD47 “don’t eat me” signal is not, by itself, enough to stimulate macrophages to attack cancer cells. Instead, the group demonstrated that blocking CD47 boosts the activity of macrophages when a second “eat me” signal is provided. This signal can be provided by certain anti-cancer antibody therapies, many of which are already approved by the FDA and in use clinically.

These findings have tremendous therapeutic implications, Ring said. “The high-affinity SIRP-alpha molecules could selectively boost the destruction of cancer cells by these antibody therapies, with increased toxicity and less damage to the healthy, non-cancerous cells.”

The authors found that their engineered SIRP-alpha molecules would enable a number of widely used antibody therapies such as rituximab (which targets certain lymphomas and leukemias), trastuzumab (which targets certain kinds of breast cancer) and cetuximab (which targets certain kinds of head and neck cancers) and colon cancer.

When physicians use an anti-cancer antibody like these to fight cancer, the patient’s body’s “don’t eat me” signal to the macrophages fighting cancer is “don’t eat me” coming from the CD47, the researchers explain. When the high-affinity SIRP-alpha binds tightly to CD47, it takes the brakes off the macrophage attack on the cancer cells.

“Physicians use an anti-cancer antibody like trastuzumab to fight breast cancer, the ‘don’t eat me’ signal from CD47 on the cancer limits the effectiveness of the antibody,” said Ring. “Potentially, any anti-cancer antibody that stimulates immune cells could benefit from this combination therapy.”

In one experiment, when either rituximab or the high-affinity SIRP-alpha molecules were used by themselves on mice with human lymphomas, they were only able to slow tumor growth. However, when the two therapies were combined, researchers found they were able to eliminate the tumors completely. “Anti-cancer antibodies are like guided missiles in terms of targeting cancer cells,” Weiskopf said. “By combining them with the high-affinity SIRP-alpha variants, you are adding high-explosive warheads to those missiles.”

The researchers hope that their work with high-affinity SIRP-alpha molecules will lead to more effective targeted-cancer therapies in the clinic. This work further validates the strategy of targeting CD47 to enhance macrophage attack of cancer,” according to Weissman. “This strategy must still be tested in humans to evaluate safety, but anti-CD47 antibodies are on schedule for the first trials in patients next year.”

Christopher Garcia

For employees of the hospitals, new ways to find Inside Stanford Medicine

Beginning with today’s issue, the electronic version of Inside Stanford Medicine will be more widely available to the staffs of Stanford Hospital & Clinics and Lucile Packard Children’s Hospital.

The electronic version of Inside Stanford Medicine now is available through SHC Connect, the intranet site for employees of the adult hospital, and through “We Are Packard Children’s,” a weekly email distributed to employees of the children’s hospital.

Inside Stanford Medicine, a twice-monthly newspaper produced by the School of Medicine’s Office of Communication & Public Affairs, provides a variety of stories about the research, clinical advances and people of Stanford Medicine. Print copies of the newspaper are distributed throughout the hospital but the electronic version goes directly to inboxes.”

Anyone who wishes to subscribe to the electronic version of Inside Stanford Medicine can visit http://med.stanford.edu/mailman/listinfo/medical-center-report and enter their information in the “subscribing section.”

To contact our editor for the paper on questions, please contact editor John Sanford at 723-8309 or at jsanford@stanford.edu. For employees of the hospitals, new ways to find Inside Stanford Medicine

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To contact our editor for the paper on questions, please contact editor John Sanford at 723-8309 or at jsanford@stanford.edu.

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Patient manages genetic high cholesterol level with nurse’s help

By Sara Wykes

Brenda Gundell’s introduction to familial hypercholesterolemia came in the 1980s. At 39, her father died of a heart attack. His total cholesterol level was 600 — well above what doctors consider to be a healthy level. Gundell, who was just 15, remembers the small, wart-like lumps that pilled out the skin near her father’s eyes, elbows and knees. She learned later that those lumps, called xanthomas, were cholesterol, accumulating throughout his body over the years.

While cholesterol is a natural and necessary part of the body’s chemistry — crucial to cell membrane function — genetic mutations can alter how it is eliminated from the bloodstream. Familial hypercholesterolemia affects cholesterol processing from birth, spreading through the cardiovascular system so perniciously that over the course of a lifetime the toll on arteries means that men with FH have a 50 percent chance of having a heart attack by age 50. Women with FH have a 25 percent chance of heart attack by age 60.

What distresses FH specialists like Stanford’s Joseph Wu, MD, PhD, is that while the condition is common and affects 600,000 in the United States, it is diagnosed in fewer than 10 percent of those who actually need it. The need for heightened awareness is clear: FH accounts for 20 percent of heart attack-related deaths in people younger than 45. This is crucial to patients like Gundell, under care for the last 17 years at Stanford Hospital & Clinics’ Preventive Cardiology Clinic, as examples of the best way to live with such a destructive, yet treatable, condition.

Shortly after her father’s death, Gundell, her sister and her four brothers had their cholesterol tested. She and two siblings had excessive cholesterol and were diagnosed with FH. FH is a genetic condition: If just one parent has it, children have a 50 percent chance of inheriting the disorder. The familial nature and the serious health consequences of FH have placed it on the Centers for Disease Control and Prevention’s tier-1 list of conditions for which testing is recommended, in particular at an early age for children of adults diagnosed with FH.

When Gundell was diagnosed, the gold standard for cholesterol reduction, a family of drugs called statins, had not yet been introduced and she took a different kind of medicine. “I really didn’t like taking the medicine, but I would take the medicine and have the blood tests. I stuck with it for a long time,” said Gundell. After some time, however, she stopped. “I said, ‘Well, I don’t see it. I don’t feel it. I’m okay.’” She went on with her life, trained as a fifth-grade teacher and married. Then, at 39, an angel that resonated with her, a pain in her elbow sent her to the doctor. At first, she thought it might be gout. She was prepared for that. Instead, her doctor told her that the painful lump was calcified cholesterol. “If it’s her left elbow, referral to her, ‘it’s everywhere,’” said Gundell. He also said he was referring her to Stanford, which had become known for its expertise in FH. This was crucial to her study and treatment of FH and other similar conditions, including those with genetic overlap.

Gundell met with Mary Ann Champagne, a clinical nurse specialist and nurse coordinator for the Preventive Cardiology Clinic. The clinic helps patients with primary prevention — managing risk factors that can lead to illness such as heart attack and stroke — and with secondary prevention, to avoid recurrence of those kinds of cardiovascular events. In Champagne, Gundell found someone with whom she could be completely honest. “I told her, ‘I’m afraid. I know I need to make changes. How can we work together so I’ll keep coming back?’” said Champagne, “We’re going to take it slow. We’re going to have you take a medicine. We’ll have you get used to it, and if we need to, we’ll adjust it. Then we’ll add another one, if we need to, and adjust it.” And that’s the way it’s gone for more than 15 years. Champagne has worked with Gundell on her non-medication options, too. Between Gundell’s attention to what she eats, and the arrival of two family dogs that needed to be walked every day, Gundell has upped her physical activity level and lost 70 pounds. “It took a while for me to accept that this is lifelong, but it is. I feel my life is valuable and I value myself, my life and what I’m doing. I want to live a long time.”

Sara Wykes is a writer for the Stanford Hospital & Clinics communications office.

OF NOTE

AMATO GIACCIA, PhD, is the recipient of a 2013 gold medal from the American Society for Radiation Oncology. The award is the society’s highest honor and recognizes distinguished members who have made outstanding contributions to the field of radiation oncology, including research, clinical, educational, and service contributions. Giaccia, who is director of the division of radiation and cancer biology at Stanford, will be honored at the society’s 55th annual meeting in Atlanta.

ROBERT SHAFER, MD, professor of medicine, and BENJAMIN PINSKY, MD, PhD, assistant professor of psychiatry and of medicine, have been recognized with awards from the Pan American Society for Clinical Virology, one of the three main professional virology organizations.

Shaf is the recipient of 2013 Ed Nowakowski Senior Memorial Clinical Virology Award, which is given to an individual whose contributions to clinical virology have had a major impact on the epidemiology, treatment or understanding of the pathogenesis of viral diseases. Much of his work focuses on the mechanisms and consequences of virus evolution, with a focus on HIV-1 therapy and drug resistance. He also created the Stanford HIV Drug Resistance Database.

Pinsky was given the 2013 Young Investigator Award, which recognizes a significant contribution to the field of clinical or diagnostic virology by an early-career researcher. Pinsky’s work focuses on the development of technologies for the molecular analysis of virus detection and identification of clinically important viruses. He also serves as director of the Clinical Virology Laboratory at Stanford. Both awards consist of a $1,000 honorarium, a prize and a plaque, and were presented at the society’s annual meeting in April.

STEWART GUNDELL, MD, has been promoted to professor of medicine and of radiology, effective May 1. His lab works on biological mechanisms of adult stem cells, embryonic stem cells and induced pluripotent stem cells. Wu also serves as co-director of the Stanford Cardiovascular Institute.

LEANNE WILLIAMS, PhD, has been appointed professor (research) of psychiatry and behavioral sciences, effective May 1. She conducts research in applied personalized neurosciences, focusing on novel ways of classifying mood, anxiety and attention disorders and of predicting treatment outcome.

EDWARD BERTACCHINI, MD, has been promoted to professor of anesthesiology, effective May 1. His research interests focus on deciphering the molecular mechanisms of anesthetic action via the techniques of computational chemistry and molecular modeling.

STEVEN COURTE, MD, has been promoted to professor of medicine, effective May 1. His work emphasizes translational clinical research involving hematologic cancers, including chronic lymphocytic leukemia. Courte also serves as vice chair of clinical affairs for the Department of Medicine.

GEORGE FISHER, MD, PhD, has been promoted to professor of medicine, effective May 1. His research program focuses on clinical trials for patients with gastrointestinal cancers. Fisher also serves as director of the Cancer Clinical Trials Office.

KIMBERLY ALLISON, MD, has been appointed professor in the Department of Pathology and of Cancer Biology at Stanford, both awards consist of a $1,000 honorarium, a prize and a plaque, and were presented at the society’s annual meeting in April.

Next senate meeting set for June 18

The next regularly scheduled meeting of the medical school’s faculty senate is set for June 18. Neil Gundheit, MD, professor of medicine and associate dean for advising, is scheduled to present a report on the results of this year’s residency match.

Hannah Valentine, MD, professor of cardiovascular medicine and senior associate dean for diversity and leadership, will give a presentation on diversity at the medical school.

Medical school faculty can download the complete minutes of previous senate meetings by visiting http://med.stanford.edu/senate.