Study points to new target for development of antidepressants

By Bruce Goldman

School of Medicine scientists have laid bare a novel molecular mechanism responsible for the most important symptom of major depression: anhedonia, the loss of the ability to experience pleasure. While their study was conducted in mice, the brain circuit involved in this newly elucidated pathway is largely identical between rodents and humans, upping the odds that the findings point toward new therapies for depression and other disorders.

Additionally, opinion leaders hailed the study’s inventive methodology, saying it may offer a much sounder approach to testing new antidepressants than the methods now routinely used by drug developers.

“While as many as one in six Americans is likely to suffer a major depression in their lifetimes, current medications either are inadequate or eventually stop working in as many as 50 percent of those for whom they’re prescribed.”

“This may be because all current medications for depression work via the same mechanisms,” said Robert Malenka, MD, PhD, the Nancy Friend Professor in Psychiatry and Behavioral Sciences. “They increase levels of one or another of two small molecules that some nerve cells in the brain use to signal one another. To get better treatment, there’s a great need to understand in greater detail the brain biology that underlies depression’s symptoms.” The study’s first author is Byungho Limm, a postdoctoral scholar in Malenka’s laboratory.

Malenka is senior author of the new study, published July 12 in *Nature*, that reveals a novel drug target by showing how a hormone known to affect appetite turns off the brain’s ability to experience pleasure when an animal is stressed. This hormone, melanocortin, signals to an ancient and almost universal apparatus deep in the brain called the reward circuit, which has evolved to guide animals toward resources, behaviors and environments — such as food, sex and warmth — that enhance their prospects for survival.

“This is the first study to suggest that we should look at the role of melanocortin in depression-related syndromes,” said Eric Nestler, MD, PhD, professor and chair of neuroscience and director of the Friedman Brain Institute at Mount Sinai School of Medicine in New York. Nestler was not involved in the study but is familiar with its contents.

The specific causes of depression are not well understood. There is no laboratory test for depression — the diagnosis is based mainly on patients’ own reports of lethargy, despondency, despair and disturbances of appetite and sleep — but a core symptom is inability to experience pleasure, a common feature of depression.

Method to sequence fetal genome uses only maternal blood

By Krista Conger

Stanford researchers have for the first time sequenced the genome of an unborn baby using only a blood sample from the mother.

The findings from the new approach, published July 4 in *Nature*, are related to research that was reported a month ago from the University of Washington. That research used a technique previously developed at Stanford to sequence a fetal genome using a blood sample from the mother, plus DNA samples from both the mother and father.

The whole genome sequencing in the new Stanford study, however, did not require DNA from the father — a significant advantage when a child’s true paternity may not be known (a situation estimated to affect as many as one in 10 births in this country) or the father may be unavailable or unwilling to provide a sample.

The new technique brings fetal genetic testing, one step closer to routine clinical use.

“We’re interested in identifying conditions that can be treated before birth, or immediately after,” said Stephen Quake, PhD, the Lee Otteson Professor in the School of Engineering and professor of bioengineering and of applied physics.

“Without such diagnoses, newborns with treatable metabolic or immune system disorders suffer until their symptoms become noticeable and

See DKA, page 7

Kale, kale, the gang’s all here

A summer farm camp helps youngsters dig into the fun of growing — and eating — fresh healthy food

By Tracie White

Kale — a form of cabbage high in beta carotene — seemed to be very important to 7-year-old Jane Jones, who grabbed the stem of a kale leaf twice the size of her head and waved it high in the air.

It was circle time at Full Circle Farm’s Summer Farm Camp in Sunnyvale one morning the last week of June where children ages 5 to 14 got the opportunity to learn about fresh, locally grown produce — where it comes from, how to grow it, how great it tastes.

And how it occasionally even makes a really great toy.

“What did we learn about yesterday?” asked counselor Ernie Bird.

“Seeds!” the kids yelled.

“And kale!” added Jane, waving her leaf even higher in the air. The group of mini-campers sat in rapt attention on log benches in the middle of an 11-acre farm in the heart of Silicon Valley, not a fast-food restaurant in sight.

“Now, walk over to the picnic tables as if you were chickens,” the instructor said, and the clucking began, elbows sticking out and flapping, as the campers waddled past the rows of broccoli and cabbage plants over to the chicken coops.

“Bawk, bawk, bawk,” they squawked.

Except Jane who kept on yelling, “Kale, kale, kale.”

It’s the second summer of what Christopher Gardner, PhD, associate professor of medicine at the Stanford Prevention Research Center, hopes will become a long-term partnership between the School of Medicine and Full Circle Farm to host the camps.

This summer, about 80 kids will rotate through. The focus of the camps is to bring kids close to the earth, teach them about gardening and open up their taste buds to the wonders of freshly grown produce.

To do it through fun activities such as food prep, craft projects, music and games. Catching consumers at an early age, that’s how to fight the obesity epidemic, says organizers of the camp.

“The challenge is to get kids to eat more healthily,” said Gardner, who has helped coordinate the partnership and stops by frequently as a camp advisor.

“We’re interested in ‘stealth nutrition.’ Telling kids to eat more vegetables just doesn’t work. Making it fun to eat vegetables does.” [For another story about Gardner’s work, see “5 questions” on page 2.]

The partnership grew out of the 2010 Food Summit at Stanford led by Gardner where the Full Circle Farm organizers showed up asking for help to get kids to be more connected to healthful foods.

The nonprofit 11-acre farm produces about 50,000 pounds of fresh produce a year and is dedicated to the renewal of local, sustainable food systems. The summer camp is an extension of this mission.

Since the Food Summit, Stanford has provided student camp counselors who come to teach and do a little science on the side. Gardner See FARM CAMP, page 4

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Alexander Berenstein, a psychologist at Stanford Children’s Health, said that he and other colleagues have noticed that parents are seeing results when they make small changes to their diet. He said that the parents who have made these changes have reported that their children are eating more fruits and vegetables, which can have a positive impact on their overall health.

“Parents are finding that by making small changes, such as adding more fruits and vegetables to their meals, they can help their children develop healthy eating habits,” Berenstein said. “It’s important to remember that small changes can make a big difference when it comes to nutrition.”

The study, which was published in the Journal of the American Medical Association, found that children who made small changes to their diet were more likely to have a lower body mass index (BMI) and a lower risk of developing obesity. The study also found that children who made small changes to their diet were more likely to have a higher intake of fruits and vegetables, which can help to prevent chronic diseases such as diabetes and heart disease.

Berenstein said that the study is important because it highlights the importance of making small changes to our diet to improve our health. He said that parents can make small changes to their diet, such as adding more fruits and vegetables to their meals, to help their children develop healthy eating habits.

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By Krista Conger

Gil Troutman is an extremely fortunate man.

In 1971, he was a new father and he had received what, only a few years earlier, would have been a death sentence: a diagnosis of Hodgkin’s disease, a malignancy of the lymph nodes.

Troutman, who was then 27 and a resident of San Carlos, Calif., heard from his doctor that research was under way at Stanford that had the potential to treat the disease. It relied on targeted radiation from a linear accelerator designed for medical use. That therapy, which was pioneered in 1962 by radiologist Henry Kaplan, MD, and oncologist Saul Rosenberg, MD, had transformed the disease into a curable one.

Fifty years after the Stanford Lymphoma Program (now the Lymphoma and Hodgkin’s Disease Research Program at the Stanford Cancer Institute) began clinical trials of this new radiation treatment, Stanford researchers and practitioners marked this milestone on July 13-14 with a symposium and patient reunion.

Troutman, his wife, Fran, and his son, Jeff (himself a Hodgkin’s survivor and Stanford patient), joined a dozen of former patients, trainees and colleagues to celebrate the anniversary of the initiation of the study, and the role played by Rosenberg since his arrival at Stanford 51 years ago. (Kaplan died in 1984.)

“It’s very simple,” said Troutman. “Without Dr. Rosenberg, I would not be here today. It means everything to me. My life, my lifestyle, my family. The ability to see my first my son, and then my grandchildren grow up.”

The cure rates for Hodgkin’s disease have gone from virtually nil to about 90 percent,” said Richard Hoppe, MD, the Henry S. Kaplan-Harry Leeson Professor of Cancer Biology. “At the time, these prospective, randomized clinical trials for lymphoma conducted by Drs. Rosenberg and Kaplan were some of the first in the world. As researchers around the world adopted this approach, we’ve furthered our understanding of lymphomas and developed new concepts of therapy, including advances in the way we use radiation, to new combinations of chemotherapeutic drugs, to monoclonal antibodies and immunotherapy. In fact, one chemotherapy regimen is known simply as the Stanford 5.

“My time at Stanford has been a blessing,” said Rosenberg, the Maureen Lyles D’Ambrogio Professor Emeritus, who noted that the success he and others have had in treating Hodgkin’s disease didn’t come as the result of a single breakthrough, but rather as a series of incremental advances. “None of our findings were initially dramatic or exciting. Progress was very gradual as we combined chemotherapy with radiation and advanced techniques on complications and outcomes. Without the patients who participated in our trials of new treatments and allowed us to observe them over decades, none of this ‘innovation’ would have been possible.”

Kaplan recruited Rosenberg, who had trained as a radiobiologist and an internist, to Stanford in 1961 from Peter Bent Brigham Hospital, Boston. Rosenberg had previously completed a fellowship at New York’s Memorial Sloan-Kettering Cancer Center, in which he established the technique of carefully evaluating and recording the outcomes of various lymphoma therapies — an approach that would be critical to the success of the Stanford 5.

When Kaplan and Rosenberg began their Hodgkin’s disease clinical trials, in which Gil Troutman would later participate, the concept of radiation for cancer treatment was in its infancy. The advent of a medical linear accelerator at Stanford in 1955 had allowed Kaplan to treat his first patient with external radiation therapy — a young boy with a tumor in his eye called retinoblastoma. The boy survived with vision intact. Kaplan wondered whether a similar therapy aimed at cancerous lymph nodes would work for Hodgkin’s disease.

Troutman called his treatment in 1971. “Dr. Kaplan was doing a study to compare the effectiveness of radiation alone, with radiation plus chemotherapy. I was in the radiation-only group. I lay on a table with lead blocks over parts of my chest, and they gave me total nodal radiation from my chin to my abdomen.”

The treatment was successful — for a time. “Everything seemed clear,” said Troutman, “but about a year after treatment, who moved to the East Coast soon after completing the treatment. But his symptoms shortly returned. Oncologists at Massachusetts General Hospital put him on a variety of chemotherapy options, including a regimen called NOPP and a single-drug treatment with a compound called vincristine. Neither eradicated the disease, however, and all of the treatments left him nauseous and exhausted. When Troutman relocated back to California, he and his wife and children moved to Stanford for help.

“Dr. Rosenberg said, ‘You know, we’ve got some new experimental chemotherapy drugs, if you’re interested in participating in a clinical trial,’” said Troutman. “I was for anything. I had three medications — adriamycin, bleomycin, vinblastine and dacarbazine (also known as ABVD) — did the trick.

“I was fortunate. In the six months, my annual check-up with Dr. Rosenberg, and everything’s been fine,” said Troutman. But even after 25 years, the family’s ordeal was not over. In 2000, Gil’s son, Jeff, then 29, began to cough. He lost energy and was unusually tired. “Hodgkin’s disease only rarely runs in families, so my doctor was doubtful that was even an issue,” said Jeff, who was 8 at the time.

“Within one week, I had my diagnosis,” said Jeff. “That was the first time in my life I’d seen my dad cry.”

“We were really shocked,” said Gil. “But there was never any question; he was going to Stanford for treatment.” To Stanford, and to Rosenberg.

Jeff underwent a new treatment — called the Stanford 5 because it was the fifth protocol in which he participated — combining chemotherapeutic drugs. Jeff had three rounds of the Stanford 5 plus four weeks of radiation. The experience was difficult, but Jeff was able to continue in some wonder side effects than those experienced by his father.

“I felt terrible, but I was nowhere near as sick as he was. I was very close to my own children after my treatment,” said Jeff, who has an 8-year-old daughter and a 5-year-old son. (Many earlier treatments left patients sterile.) “I owe a tremendous debt to Dr. Rosenberg for making it possible to have the family I have.’

“Thanks to Dr. Rosenberg, and Jeff and I go together now for check-ups, and it’s always wonderful to see him. He keeps saying he’s going to retire, but not yet.”

Rosenberg’s influence extends beyond lymphoma, however. “He essentially re- established the field of medical oncology at Stanford,” said Hoppe, “and he has mentored many, many other oncologists who now lead similar programs around the country. He’s been a wonderful professor and teacher, and it’s a joy for the medical students to have the opportunity to learn from him.”

Sometimes Jeff Troutman, who now works in the construction by volunteering to be a sample patient for trainees. “Dr. Rosenberg is always on the lookout to see if the doctors he’s bringing in have anyاوري or is there a needle in the haystack? Now he’s retired, and he’s always making sure people are aware of the need for research funding. “I’m sorry to see that you’re in great shape. I’ll see you in a year if I haven’t retired or died.”

“There are three things: someone like me leaves behind: my children, my students and trainees, and my patients and their families,” said Rosenberg. “These wonderful results continue to expand and grow over time. Nothing can be more satisfying.”

Celebration marks 50 years of treating Hodgkin’s disease

Evaluate

continued from page 2

or both, will talk with the physician about alternative practices and the medication of requested privileges, including the possibility of revocation of privileges, Pizano said.

“Healthcare providers’ duty is to be supportive and respectful of physicians’ careers and contributions and to suggest resources to assist them while also being mindful of the patient’s rights and needs and child outcomes and children for whom we have the privilege to provide medical care,” he said.

In past conversations about the policy, the Medical Staff Services Department at 497-8920.

High demand for blood at community hospitals

With a recent surge in blood use for community hospitals — particularly Rh-negative blood — officials at the Stanford Blood Center are encouraging people to donate blood during the summer months.

Center administrator Harpreet Sandhu said the frequency of auto accidents and surgeries in the summer increases the demand for blood. At the same time, the center loses many valuable donors because colleges and high schools are out of session and many people leave for vacations. During the school year, high school mobile drives play a significant role in keeping inventory up, she said. Approximately 20 percent of the center’s blood products come from mobile drives. Of those, an estimated 90-95 percent are high school students participating in mobile drives.

Sandhu said the demand is linked to the unique needs of the hospitals served by the Stanford Blood Center, including Stanford Hospital and Lucile Packard Children’s Hospital, which perform many complex, high-risk procedures and treatments that require a lot of blood products — particularly for preemies, cancer patients and transplant recipients.

Liver transplant, for example, sometimes requires 40 or more units of blood. While some hospitals donate 40-50 units of blood every day, others have no regular donors. In cases such as these, more donors are needed, Sandhu said, they donate a relatively small portion of the community. An estimated 39 percent of the population nationwide is eligible to donate, but only about 5 percent in California give regularly. She urged anyone able to donate to consider helping out this summer, adding that while the need for Rh-negative blood is particularly among children, more is needed as well.

To encourage donations, the blood center will offer a variety of incentives, including complimentary movie tickets, coupons for free ice cream and a tie-dyed T-shirt.

Donors should be at least 16 years old with no cold or flu symptoms. They must eat well prior to donation, drink fluids and present photo identification at the time of donation. The process takes about an hour. For more information or to schedule an appointment, online, please call (888) 723-7831 or visit http://bloodcenter.stanford.edu.

By John Sanford is a writer in the communications office at Stanford Hospital & Clinics.

For more information, call the Medical Staff Services Department at 497-8920.
VA health system opens new 80-bed mental health center

The Veterans Affairs Palo Alto Health Care System officially opened June 22 a new 80-bed acute mental health center on its campus on Miranda Avenue.

“This new facility will ensure that California’s veterans continue to have access to high-quality mental health care that they earned through their service to our nation,” said Department of Veterans Affairs Undersecretary for Health Robert Petzel, MD. "This is a priority for the American people. It’s a priority for the Department of Veterans Affairs." The new center will provide a continuum of mental health services, from inpatient to outpatient, with an additional research component. The 90,000-square-foot facility will house four units, each with 20 inpatient acute psychiatric beds. The project also features outdoor enclosed gardens for the patients and a separate mental health research and office pavilion. Most rooms are private, with some semi-private, and all have private bathrooms.

“This new facility is like day and night to the current one,” said Christopher Hurt, 25, an Iraq War combat veteran and patient. “I’ve heard other people say they’ve never seen a facility like this one. It’s bright, airy and just makes the healing process so much nicer. It even has a workout room and basketball court. I love it.”

The building’s therapeutic design and healing environments were the result of collaboration with clinicians and considering the perspective of the veterans who will receive care in the facility. To enhance the treatment of veterans, it includes patient access to landscaped gardens, ample use of natural light in all internal patient and staff areas and views to landscaped areas from all patient bedrooms.

Last year, VA provided quality, specialty mental health services to 1.3 million veterans. Since 2009, VA has increased the mental health care budget by 39 percent. Since 2007, VA has seen a 35 percent increase in the number of veterans receiving mental health services and a 41 percent increase in mental health staff. In April, as part of an ongoing review of mental health operations, Secretary of Veterans Affairs Eric Shinseki announced VA would add approximately 1,600 mental health clinicians as well as nearly 300 support staff to its existing workforce of 20,590 to help meet the increased demand for mental health services. The additional staff would include nurses, psychologists, psychiatrists and social workers.

VA’s executive director, Full Circle Farm’s executive director. “Now they’re eating kale, cauliflower, broccoli. The kids bring the produce home, and parents are encouraged to cook with it. What they grow ends up in their dinner salad.”

Gustavo Chavez, a 20-year-old human biology student and camp counselor, knows firsthand how excited the kids get about the fresh produce, but he also wants to document the success of the farm so that similar camps can be developed. “When kids can pick it out of the garden themselves, they get excited,” he said. He’s collaborating with other Stanford interns to document their work. They hope to publish a paper on how farm camps can encourage good nutrition in kids.

“As a nutrition scientist, what I do doesn’t necessarily help with this. Research like I’ve done on how garlic helps or hurts your cholesterol doesn’t help. Getting out into the community and changing behavior, that’s what works.”

Getting out into the community can help increase children’s interest in healthy eating. “We hear from parents who say, ‘Oh my gosh, all my kids would never eat peanut butter!’” said Wolfram Alderson, a man biology student and camp counselor. “Last month’s campers aged 5 to 7 were a particularly young group of future consumers, with a notable fascination for the food at snack time. They nibbled around the edges of cucumbers, studied the freshly cut corn, and boasted about their homemade rolled tortillas. Pretty much every young camper tried something new at the camp, with jicama becoming a new snack-time favorite. ‘Yeah, I like farm camp,’ said Tobias Poulus, 7, nodding his head. ‘I like to water vegetables. The corn today was very sweet.’ He’ll even occasionally eat some jicama when he has the time. Then he hopped up and down on one foot and ran off to help make the tortillas. “We hear from parents who say, ‘Oh my gosh, all my kids would never eat peanut butter!’” said Wolfram Alderson,” Full Circle Farm’s executive director. “Now they’re eating kale, cauliflower, broccoli. The kids bring the produce home, and parents are encouraged to cook with it. What they grow ends up in their dinner salad.”

Gustavo Chavez, a 20-year-old human biology student and camp counselor, knows firsthand how excited the kids get about the fresh produce, but he also wants to document the success of the farm so that similar camps can be developed. “When kids can pick it out of the garden themselves, they get excited,” he said. He’s collaborating with other Stanford interns to document their work. They hope to publish a paper on how farm camps can encourage good nutrition in kids. The scientific question is, will a garden-based education change behavior? Chavez said. “The goal is to change early childhood behavior. We definitely have a lot of health problems among kids in our society — growing rates of obesity, diabetes. Children don’t eat a lot of veggies. We’re collecting various data to show how this camp affects behavior.”

Money for the camp goes directly back to the farm to keep it sustainable. Full Circle Farm is also able to give half the kids full scholarships. (The camps run one to two weeks and costs range from $195 to $295.) Information about the camp is available online at http://www.fullcirclesunnyvale.org.
Novel surgery at Packard Children’s repairs boy’s airway, voice box

By Erin Digitale

Noah Jackson was born without a voice. Because of a rare genetic disease, his airway was so narrow he couldn’t cry at birth. In fact, he could scarcely breathe, and had surgery at 5 days old to implant a tracheotomy tube that let air pass through a hole in his throat. Cuddling their newborn, parents KC and Rebecca knew Noah’s only hope for someday speaking and breathing normally lay in the possibility that his voice box could be surgically reconstructed later on.

In the summer of 2010, when Noah was 18 months old, his surgeon at home in Fresno, Calif., referred him to Packard Children’s world-class otolaryngology team, including Peter Koltai, MD, who is experienced at reconstruction of the voice box. But even this considerable surgical expertise provided no guarantee of success.

“This was a complete obstruction, as bad as it gets,” said Koltai, remembering his early assessments of Noah’s airway. “There was no opening at all to his voice box.” After the “trach” tube was placed, Noah’s airway had scarred shut. When Koltai first evaluated Noah, no air came down from his nose or mouth to his lungs.

Noah also faced other difficulties. His rare genetic disease, Fraser Syndrome, causes structural anomalies in many parts of the body. Noah has only one eye, and was born with hand, foot and digestive-tract problems that required surgery in infancy. But the trach was Noah’s biggest medical challenge. The tube dislodged about once a month, leaving Noah breathless and sparking anxiety for his family.

“Every time he played, we were constantly watching the trach,” Rebecca said. If the tube came out when a caregiver was turned, Noah could not say help; he communicated only in sign language.

Koltai’s attempt to free Noah from the trach and give him a voice was a multi-stage undertaking with an estimated 70 percent chance of success. By November 2010, Noah was ready for the reconstruction surgery. Koltai and his team opened Noah’s voice box and removed the scar tissue that blocked Noah’s airway.

“The scar came up to the bottom of the vocal cords, but we were able to dissect them free,” Koltai said. The team then used two pieces of rib cartilage from Noah’s chest to enlarge the framework of the voice box. The new airway was supported with a stent inserted through the center; Noah would keep breathing through his trach until the airway was fully functional.

A month after the stent was removed, Noah had a check-up.

“The reconstruction had worked well below the level of the vocal cords,” Koltai said, but problems remained. “Because the vocal cords had been involved in scarring, they had fused back down like a zipper, almost totally closed,” he added, explaining that this not only prevented Noah from speaking, but also jeopardized his ability to breathe normally. Fortunately, there was still a small opening. Over the next four months, the team repeatedly inserted a high pressure airway balloon of Koltai’s own design that gradually re-opened the airway and allowed the vocal cords to heal in a normal configuration.

Gradually, Noah learned to breathe through his nose and mouth. “Having a trach, the air just kind of dumps in and oozes out,” Rebecca said. Noah’s speech and sign-language therapists helped him build lung power with toys such as pinwheels to blow. It was hard work.

In June 2011, Koltai re-examined Noah’s airway. “I’ll never forget it,” Rebecca said. “Dr. Koltai came running out and said ‘Do you want the good news or the good news? I’m going to take the trach out right now!’”

A few minutes later, with Noah seated on Rebecca’s lap, Koltai undid the Velcro straps that held the trach in place. The little boy breathed: in and out, in and out. Noah seemed bewildered by the

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Summer issue of magazine explores science’s data deluge

By Rosanne Spector

Just as people leave digital trails these days, so do our cells — and they’ve been doing so for decades as a result of biomedical research. This data, much of it stored in genetic transcripts in huge public databases, constitutes a goldmine for research and drug development.

But the magnitude of the data, the speed at which it’s growing and the threat it could pose to individual privacy mean managing “big data” is one of biomedicine’s most pressing challenges.

The potential for big data in medical science is the theme of a special report in the summer issue of Stanford Medicine magazine.

“Hiding within those mounds of data is knowledge that could change the life of a patient, or change the world,” said data miner Atul Butte, MD, PhD, an associate professor of pediatrics, in an article in this issue. “If I don’t analyze those data and show others how to do it, too, I fear that no one will.”

The report’s opening article tells about a project launched by the chair of Stanford’s Genetics Department, Michael Snyder, PhD, to generate billions of individual data points about his own physiology and then analyze them. The results, about 30 terabytes of data — about 30,000 gigabytes, or enough to store a file of high-quality audio to play non-stop for seven years. He hopes that data collections such as his will become commonplace tools to personalize health care. He submitted his personal data to public databases, though he realizes many others who have their genomes sequenced will not make this choice.

The data boom is not only molecular. Health information that can be gleaned from patient records is another rich resource. Another special report shows that Stanford University Medical Center is among a handful of biomedical institutions building research databases based on their patients’ information so their researchers can use them to improve medical care.

The federal government is responding to the abundance of data with funding to support its development as a resource: In March, the Obama administration announced the Big Data Research and Development Initiative, committing $200 million to “greatly improve the tools and techniques needed to access, organize and glean discoveries from huge volumes of digital data.”

The abundance of data could change how biomedical scientists conceive of their experiments in the first place. Hypothesis-driven science isn’t dead, say many scientists, but it’s not the most useful way to analyze big data sets.

“We’ve been so focused on generating hypotheses,” said cardiologist Evan Ashley, MD, in the report’s lead article. “But the availability of big data sets allows the data to speak to you. Meaningful things can pop out that you hadn’t expected. In contrast, with a hypothesis, you’re never going to be truly surprised at your result.”

Inside the report:

• The lead article on the data deluge in biomedicine, told through the story of genetics professor Michael Snyder, who made himself the subject of his own big-data project, allowing the world to watch as his health took a nosedive.

• A piece on the creation of a research database built on medical records from Stanford and Lucile Packard Children’s hospitals.

• A profile of wildly successful medical data miner Atul Butte, who’s urging other researchers to dig in.

• An article on the rise in importance of bioinformatics: Suddenly the “oddball” old field of statistics is where the action is.

• A Q&A with author Vernon Vinge, five-time winner of science fiction’s most prestigious honor, the Hugo Award. His stories explore themes including deep space and the “technological singularity,” a term he coined for the emergence of a greater-than-human intelligence brought about by the advance of technology.

This issue’s “Plus” section, featuring stories unrelated to the special report, includes:

• A story on using gamification with a computer game called “Diabetes” to teach residents and doctors how to recognize when patients have sepsis, and how to treat them.

• A feature on the mounting evidence that a single antibody, known as anti-CD47, could knock out many cancers.

The magazine, including Web-only features, is available online at http://stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at 736-0297 or medmag@stanford.edu.

Stanford Medicine is published three times a year by the medical school’s Office of Communication & Public Affairs. Follow @stanmedmag on Twitter.
Malenka continued from page 1

and is often known as the blues.

In their search for new compounds to combat depression, however, drug developers typically have used tests of mouse behavior that do not have a key feature of depression — and may also limit the search for effective drugs. “Not all animal models are created equal,” said Malenka.

In this study, Malenka and his colleagues tested sets of drugs to experience enjoyment. In another departure from more common practice in studies of depression, the scientists conducted their molecular and behavioral assessments after exposing the mice to chronic stress — the kind that we humans experience all the time and that is associated with a loss of the ability to experience happiness, even in otherwise happy, normal mice in a single stressful situation.

“Depression in people often involves chronic stress,” commented Nestler. “Tossing a person in a swimming pool and telling him to swim doesn’t induce despair.”

Yet it is precisely tests of this type that have been primarily used in the pharmaceutical industry’s hunt for new antidepressants. Common animal assays of depression involve placing normal animals in a swimming pool to try to measure observable outcomes. One example is the “forced-swim” test: throwing a rat or a mouse into water and measuring how long it takes for the animal to get out of the water. Largely, however, mice are forced to struggle, single doses of these drugs are never effective in people. “We wanted to find out, because we were wondering if by modulating melanocortin’s activity with a drug we could relieve or prevent a major symptom of depression.”

Malenka’s team subjected mice to chronic stress by confining them, for three to four hours a day, in small, conical tubes with holes in them for air flow but no source of food or water. This confinement clearly reduced the mice’s preference for sugar water over plain water. (The animals also lost about 5-10 percent of their body weight, a frequent depression symptom.)

Rather than simply noting the altered sugar preference behaviors in the stressed mice, the investigators used electrophysiological, biochemical and gene-transferring techniques to manipulate and, ultimately, to delineate the precise brain circuitry involved in the stress-elicited behavioral changes right down to the molecular level.

For example, the researchers scrutinized the nerve cells in the nucleus accumbens that contain receptors for melanocortin. Those nerve cells receive signals from a melanocortin-secreting nerve tract that impinges on them. They found that both chronic stress and the direct administration of melanocortin diminished the signaling strength of some of the tiny electrochemical contacts, known as synapses, on a set of nerve cells in the nucleus accumbens that contain receptors for melanocortin. When these receptors were removed using a sophisticated laboratory trick, the same stressful confinement no longer caused changes in those nerve cells’ synapses. Simultaneously, despite the week-long stressful experience, the mice’s sugar preference was restored to normal. Finally, the animals no longer lost weight.

To test whether preventing these stress-elicited biochemical changes in the brain also reduced the effects of stress on the mice’s behavioral response to things besides food and sugar, the researchers and their colleagues reared the mice with sucrose, which they got the same constellation of results with cocaine as they had in their earlier experimentation — further strong evidence that the changes in the brain due to melanocortin action cause an animal to lose its ability to experience pleasure.

Importantly, Malenka and his associates also demonstrated that the brain circuitry involved in the stress reaction to the forced-swim test remained when the bells went off. Manipulating the melanocortin-associated pathway in the nucleus accumbens had no effect on the response to the forced-swim test. The stressed mice gave up just as easily when the melanocortin receptors in their nucleus accumbens were depleted as when they weren’t.

By looking at the circuits and mechanisms underlying anhedonia, Malenka and his associates thus avoided a pitfall of research on mental diseases, said Hyman. “This study shows how animal research ought to be done.”

The melanocortin pathway is already of interest to drug companies. Malenka said that several researchers are trying to develop drugs that target appetite disorders. So companies already have melanocortin mimics and inhibitors that are in preclinical testing. And researchers are doing clinical tests to determine whether managing patients’ melanocortin signaling dimishes the risk of depression. This could have implications beyond treatments for depression because anhedonia manifests in other neuropsychiatric syndromes, such as addiction, that similarly affect unusually ill people who have given up hope.

Additional study co-authors were under- graduate scholars Brad Grueter, Ph.D., and Patrick Rothwell, Ph.D. The study was supported by the National Institute on Aging, the National Institute of Mental Health and the Davis Foundation Program in Eating Disorders Research. The Department of Psychiatry and Behavioral Sciences also supported this work.
**Quake continued from page 1**

cases determined." Quake is the senior author of the research. Former graduate student Yair Blumenfeld, MD, is now a senior scientist at ImmuNexx, and current graduate student Wei Gu are co-first authors of the article.

As the cost of such technology continues to drop, it will become increasingly common to diagnose genetic diseases within the first trimester of pregnancy, the researchers believe. In fact, they showed that sequencing just the exome, the coding sequence of the genome, can provide clinically relevant information.

In the new study, the researchers were able to procure and sequence both sequences they obtained to determine that a fetus had DiGeorge syndrome, which is caused by a short deletion of chromosome 22. Although the exact symptoms and their severity can vary among affected individuals, it is associated with cardiac and neuroectodermal problems, as well as cognitive impairment.

Newborns with the condition can have significant feeding difficulties, heart defects and convulsions due to excessive amounts of circulating fetal chromosomal material from both the mother and the fetus. They also detect only a limited number of genetic conditions. The new technique hinges on the fact that pregnant women have DNA from both cells and the cells of their fetus circulating freely in their blood. In fact, the amount of circulating fetal DNA increases steadily during pregnancy, and late in the trimester can be as high as 30 percent of the total. In 2008, Quake's lab pioneered the use of the relative levels of fetal DNA in maternal blood to diagnose conditions caused by missing or extra chromosomes, such as Down syndrome. Four companies in the United States now market tests based on the technique to physicians and parents, and demand for the service is increasing steadily. (Quake's specific approach was licensed by Stanford to Redwood City-based Verinata and South San Francisco-based Fluidigm Inc. Neither company was involved in the new study.)

Prenatal diagnosis is not new. For decades, women have undergone amniocentesis or chorionic villus sampling in an attempt to learn whether their fetus carries genetic abnormalities. These tests rely on obtaining cells or tissue from the fetus through a needle inserted in the uterus—a procedure that can itself lead to miscarriage in about one in 200 pregnancies. They also detect only a limited number of genetic conditions.

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This study takes the blood-sampling test one step farther by recognizing that circulating fetal DNA contains genetic material from both the mother and the fetus. By comparing the relative levels in the mother's blood of regions of material (from both the mother and the fetus) and paternal (from the fetus only) DNA known as haplotypes, the researchers were able to identify fetal DNA from the mix and isolate it for sequencing. The method differs from that of the University of Washington group by inferring the father's genetic contribution, rather than sampling it directly (through saliva).

The Stanford team tried its method in two pregnancies. One of the mothers had DiGeorge syndrome; the other did not. Their whole genome and exome sequencing showed that the child of the woman with DiGeorge syndrome would also have the disorder. The finding was confirmed by comparing the predicted fetal genome sequence with the sequence obtained immediately after birth from umbilical cord blood. Although the experiments were performed retrospectively and these women and their babies were not involved, the Stanfo study is finding in a real clinical setting would likely prompt doctors to assess the baby's heart health and calcium levels shortly after birth.

"Three years ago we were very excited to find successfully non-invasive fetal aneuploidy detection," said study co-author Yair Blumenfeld, MD, a clinical assistant professor of obstetric and reproductive medicine at Stanford School of Medicine. "But we always knew that detecting fetal chromosomal abnormalities was just the tip of the iceberg. The ability to diagnose individual gene defects was the future. This important study confirms our ability to detect individual fetal gene defects simply by testing mom's blood." The researchers plan to continue to develop the technology for eventual use in the clinic.

In addition to Quake, Gu, Fan and Blumenfeld, other Stanford scientists involved in the research include graduate student Jianbin Wang and professor of obstetrics and gynecology Yasser El-Sayed, PhD.

The research was funded with support from the Howard Hughes Medical Institute and the National Institutes of Health.

Quake and Fan hold shares in Veri nata Health and Fluidigm. Quake is also co-founder and chief scientific officer of Bioengineering, which is run jointly by the schools of Engineering and of Medicine.

**Airway continued from page 5**

the adults around him.

The fact that he leads a renowned sut gery and neuroscience group makes it all the more surprising that children’s airways didn’t diminish Kol tani’s enjoyment of the moment. "It gives you those bumps every time it works," he said.

Noah’s life is now much like that of any 3-year-old. He can roughhouse with friends without risk of dislodging a trach tube. He can play in his room while his parents keep an ear out from around the corner. He attends preschool, and is hitting cognitive and development milestones on schedule. And he is talking, “His voice will probably always be on the quiet and raspy side, but he’s understandable,” Rebecca said. “That’s huge.” For Rebecca and her husband, KC, it’s a dramatic change from their son’s early days when they focused on his medical care. Now they can think and dream about what lies ahead for him. If your infant has complex medical needs, said Rebecca, “it’s scary to think about the future, so you just don’t. You don’t think, ‘What’s going to happen to my child when he’s 16?’ Noah, it turns out, has plenty to say about his future. He loves visiting the Monterey Bay Aquarium and recently told his parents that when he grows up he wants to work with fish. He’ll be a little while before Noah is ready for his career in marine biology. But in the meantime, he’s happy to chat about his favorite species of sharks—or whales, or turtles, or jellyfish, or sea horses.

July 19-22 conference delves into science of compassion

Stanford medical school's Center for Compassion and Altruism Research and Education is presenting a major conference, "Empathy, compassion and the brain: recent advances in research on compassion, altruism, social connection and service."

Researchers and members of the public can now register for the event, which is taking place in Telluride, Colo.

"The science of compassion: Origins, mechanisms, interventions" will gather leading psychologists, neuroscientists, theologians, computer scientists and experts from many disciplines who are working in research sessions. Findings will explore the origins of compassion as well as compassion in action, how it can be measured and how we can foster it through interventions.

Invited speakers include Philip Zimbardo, PhD, professor emeritus of psychology at Stanford, and keynote speaker Richard Davidson, PhD, a pioneering researcher on meditation and brain function. Other invited speakers include scholar Tshotep Jinpa Langri, His Holiness the Dalai Lama’s long-time translator. Compassion meditation opportunities, practices and interactive workshops will be offered between sessions.

"While compassion is a fundamental part of every religious tradition, there is an ever-increasing body of scientific evidence that being compassionate has immense positive impact on the individual both in regard to their mental and physical health," said James Quakenbush, PhD, director of the Stanford researc h center, known as C-CARE, and clinical professor of neurology. "We at C-CARE are very excited to sponsor the conference and contribute to this expanding field."

Event co-sponsors include the Telluride Institute, the University of California-Berkeley’s Great Good Science Center, the University of Wisconsin’s Center for Investigating Healthy Minds and the Swedish Association for Contemplation in Education and Research. American Psychological Association-approved continuing education units are available to psychologists and master’s level clinicians, with one credit issued per hour of conference attendance.

Seating is limited. For more information about the cost of the conference and to register, visit http://ccare.stanford.edu/telluride. For questions and media inquiries, please contact Emma Seppala at emma@stan ford.edu or 723-3548.

Preceding the conference on July 18 and 19, the Telluride Institute will host a compassion festival to discuss methods to increase compassionate interaction in regional communities. Information and tickets are available at www.compassion-festival.org.

Follow the Science of Compassion on Facebook and the Huffington Post website.

Researchers retract paper from 'PLOS Medicine'

Stanford researchers Raja Bar naji, MD, and Eran Bendavid, MD, have retracted a study published May 8 in the journal PLOS Medicine.

The findings, presented in the essay, "Does development assistance for health really displace government health spending? Reassessing the evidence," contained errors in statistical model choice and reporting.

The essay was featured in a Stanford University news story released May 8 titled "Stanford study shows no evidence that internation al development assistance for health leads to displacement of public health spending by recipient government.

The Stanford researchers erroneously concluded that there was no significant displacement of foreign aid.

Barnaji is a physician at Stanford Hospital & Clinics and an affiliated scholar of the Center on Democracy, Development and the Rule of Law at the university’s Freeman Spogli Institute for International Studies. Bendavid is an assistant professor of medicine and an affiliate of FS’ Institute for Global Studies.

When the researchers discovered their mistake, they informed editors at PLOS Medicine, who agreed to retract the record. The editors agreed with the need for the retraction and accepted the authors’ explanation of their error.

The retraction was published on the journal website in late June.

Stephen Quake and colleagues have devised a new method to sequence an entire fetal genome using only a blood sample from the mother. The test could someday be an alternative to amniocentesis.

Researcher retracted paper from 'PLOS Medicine'
A workshop advances U.S. health data network

By Bruce Goldman

A workshop to foster the development of a U.S. health data network was held in Stanford, Calif., on July 2-3 in Arrillaga Alumni Center, was sponsored by the U.S. Patient-Centered Outcomes Research Institute (PCORI), and drew 100 invited participants from across the country, representing almost every domain involved in health research: clinical researchers, bioinformatics experts, social-media mavens, patients, patient advocates, pharmaceutical-industry representatives, software developers, ethicists, government regulators, insurance payers and legal scholars. PCORI, with an annual budget of about $50 million, was established as an independent, nonprofit research organization under the Patient Protection and Affordable Care Act of 2010. Its mission is to conduct and disseminate medical research that directly informs patients’ and providers’ health-care decisions.

The workshop is designed to provide guidance to PCORI on how to efficiently target its research investments and form partnerships to make the best use of the many burgeoning islands of electronic data. True form of a diverse multitude of research networks and thousands of providers using electronic medical records — to produce a coherent system that can generate valuable information critical for health-care decisions — said the workshop’s organizer, Steven Goodman, MD, PhD, a Stanford professor of medicine and health policy and polyclinic, and a member of the PCORI board of governors.

Creating the underlying electronic infrastructure to achieve this is an enormous challenge, Goodman said. “We have no good way to capture health outcomes on patients over time, and different electronic systems code diseases, treatments, outcomes and patient characteristics differently.”

“The successful establishment of such a network could be PCORI’s most significant contribution and enduring legacy,” said Collins, who sits on PCORI’s board of governors. PCORI executive director Joe Selby, MD, PhD, noted that a well-designed information system will be competent not just to learn what works best, but also to feed back to the health system, rapidly disseminating these findings in what is targeted as a four-way relationship between patients and providers. “It’s got to be a two-way street,” Selby said.

During the course of the two-day session, the discussion moved from aggregating electronic health-record data for research to how to harness the power of activated patient networks through social media, and how to use smart phones both to record patient experience in real time and as activity sensors. Aggregating large numbers of patients in these networks holds immense potential for analyzing rare diseases, guiding therapies’ effectiveness in different patient subgroups and tracking the progress of patients under different treatment regimes. But of equal importance, participants said, is putting patients at the center by facilitating affordable, efficient care; quickly pushing health information to those who need it; and obtaining patients’ informed consent to use their health information for studies that haven’t even been conceived of yet. Earning patients’ trust is essential and will require their involvement in the leadership of these initiatives and the formulation of research questions, workshop participants said.

This research need not be limited to the effects of drugs and devices. “How health-care delivery is organized may determine its success more than what drug you get,” said Goodman. “Is an appointment reminder system in place? Are there nurse-practitioners available for advice whenever it’s needed?”

Another challenge participants addressed was the publish-or-perish paradigm that discourages researchers from parting with their work to the public; this might be broken during epileptic seizures.

The workshop advanced U.S. health data network through digital data networks, and in developing functional infrastructure to achieve translational research strategies for better preventing and managing postpartum hemorrhage.

Alexander Chang, MD, has been promoted to associate professor of radiation oncology as of June 1. He is interested in developing stereotactic body radiotherapy for tumors of the liver, both primary and metastatic, and in developing functional imaging as a means of determining treatment response with radiation. Other interests include developing image-guided radiosurgery to improve radiation delivery for GI cancers.

Daniel Chang, MD, has been promoted to associate professor of medicine as of June 1. Her research interests include international health policy, pulmonary infectious diseases and strategic planning for global health catastrophes, with a focus on international pandemic influenza mitigation strategies.

Cesar Lopez Angel, a medical student and PhD candidate in immunology, has received a 2012 and Daisy Soros Fellowships for New Americans. Fellows receive tuition and living expenses of up to $90,000 over two academic years for study at a U.S. university. The fellowships were established for the children of immigrants and are awarded for creativity, originality, initiative and sustained accomplishment. Lopez Angel is studying the influence of age on T-cell function in the lab of Mark Davis, PhD, a professor of microbiology and immunology, and has worked with Stanford’s free clinic.

Joseph Parviz, MD, PhD, has been promoted to associate professor of neurology and neurological sciences as of June 1. His research focuses on the field of health trajectory. In his cognitive theory, he conducts interdisciplinary research to understand patient health literacy as potentially modifiable determinants of child health disparities, especially in chronic illness and special health-care needs.

GARRETT ANDERSON, PhD, postdoctoral scholar in neuroscience, and DEAN CARLSON, PhD, postdoctoral scholar in psychiatric and behavioral sciences, have each been awarded an Autism Speaks Postdoctoral Fellowship in Translational Research. Anderson received $108,700 to study the role of the CNTNAP2 gene in normal cognitive and social development and synaptic transmission. Carlson received $104,200 to conduct a randomized, controlled trial of oxytocin treatment for social deficits in children. Autism is a diverse group of lifelong developmental disorders characterized by highly variable symptoms and needs for duration of construction.

Alexander Butwick, MBBS, FRCA, MS, has been appointed assistant professor of anesthesia as of June 1. His research interests include international anesthesia, opioid pain, pain science and education, and anesthesia for surgery in Africa. Butwick is a recipient of the Stanford Medical Scientist Research Scholar award.

The workshop featured presentations, group discussions and visits to Stanford’s medical school and hospitals.

The workshop was sponsored by the American Academy of Dermatology, the U.S. Department of Defense, the U.S. Patient-Centered Outcomes Research Institute, the U.S. Department of Veterans Affairs, the U.S. National Institutes of Health and the U.S. Food and Drug Administration. It was cosponsored by the American Society for Medical Geomatics and the European Society for Medical Geomatics.

Workshop advances U.S. health data network

OF NOTE

Reports on significant medical and awards for faculty, staff and students

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Sculplture moved to allow for temporary parking

The distinctive Mihiko metal sculp- ture, once situated outside the Cen- ter for Behavioral Sciences Research, has been relocated in anticipation of changes to the site. The 29-foot sculp- ture by San Francisco artist Carl di Suvero has a new home on the Gov- ernor’s Lawn near the Clark Center on Campus Drive.

While the site will ultimately be used for the construction of a new school building known as Foundations in Medicine 1, the sculp- ture’s move now comes because of temporary parking needs for Stan- ford’s hospital and other uses of its new facilities. As part of an effort to address the problem, the medical school took over the existing parking lot next to the lawn area outside the CCSR for valet parking for hospital visitors. The site will be converted to a pediatric parking area with valet space for 168 cars.

The school agreed to step in after it became clear that the hospital would be strapped for space later this year. The hospital is scheduled to demolish Parking Structure No. 3 on Blake Wilbur Drive. A new parking area at Hoover and the conversion of Parking Structure No. 4 later this year will fill that void.

Plans now call for construction of the temporary valet-parking lot during the week of August 13 to 15, with the even more limited lot in mid-September. The temporary lot will be removed in a few weeks, when the new foundations building begins on the FMI project.

Memorial service for Forthmayr on July 26

A memorial service will take place on campus July 26 for Henn Forth- mayr, MD, a professor emeritus of neurology and medical director of the Stanford Neurology Clinic, who died May 1 while hiking in Nepal.

The service will begin at 4 p.m. in Stanford’s Memorial Church and is open to all who would like to attend. Among those paying tribute will be Stephen Malli, MD, professor and chair of pathology. A reception will follow at 5:30 p.m. at the Faculty Club.

Forthmayr was an expert on medieval European parking spaces in the Treisdrider pay lot, located in the second row from May- field Avenue. He said that the parking spaces are full, dashboard permits may be purchased from the pay kiosk in the lot, and parking is $6 per day. Permits are $80 for temporary parking (to purchased permits need only last un- til 4 p.m.) For questions about park- ing and access, call the main church number at 723-1762.

LLEI SANDERS, MD, has been ap- pointed associate professor of pediatrics as of June 1. His research focuses on the field of health trajectory. In his cognitive theory, he conducts interdisciplinary research to understand patient health literacy as potentially modifiable determinants of child health disparities, especially in chronic illness and special health-care needs.

ALEXANDER BUTWICK, MD, PhD, a postdoctoral scholar, received the 2012 American Society for Medical Geomatics postdoctoral fellowship award, a $50,000 grant that encourages junior researchers to pursue a career in geomatics while supporting their research during their fellowship training. He studies the role of the phosphatidylinositol 3-kinase pathway in cutaneous T-cell lymphoma.

July 10, 2012

INSIDE STANFORD MEDICINE