Seung Kim and fellow researchers discovered a hormone they call limostatin — after the Greek goddess of starvation, Limos — in fruit flies. It tamps down circulating insulin levels during recovery from fasting or starvation. They also found a protein with a similar function in humans.

By Krista Conger

n insulin-regulating hormone that, until now, only had been postulated to exist has been identified by researchers at the School of Medicine. The hormone, called limostatin after the Greek goddess of starvation, Limos, tamps down circulating insulin levels during recovery from fasting or starvation. In this way, it ensures that precious nutrients remain in the blood long enough to rebuild starving tissues, rather than being rapidly squirreled away into less-accessible fat cells.

The researchers first discovered limostatin in fruit flies but then quickly identified a protein with a similar function in humans. "Starvation or famine is an ancient, ever-present threat that these disorders share some common potential way to regulate insulin output in humans." In particular, members of a family with an inherited mutation in the human analog of limostatin exhibited many of the same physiological characteristics as flies genetically engineered to be unable to produce limostatin — namely, high levels of circulating insulin, low blood sugar levels and a tendency toward early onset obesity.

A paper describing the research findings was published Feb. 3 in Cell Metabolism. Kim is the senior author, and graduate student Ronald Alfa is the lead author.

By Bruce Goldman

In a study analyzing whole-brain images from nearly 16,000 people, researchers at the School of Medicine identified a common pattern across a spectrum of psychiatric disorders that are widely perceived to be quite distinct.

The meta-analysis of 193 peer-reviewed papers, published Feb. 4 in JAMA Psychiatry, reports a loss of gray matter in three brain structures that, although physically separate, participate in a network associated with high-level functions, including planning and decision-making.

The findings call into question a longstanding tendency to distinguish psychiatric disorders chiefly by their symptoms rather than their underlying brain pathology.

In any given year, nearly one in five Americans meets the criteria for a diagnosis of psychiatric illness. "The idea that these disorders share some common brain architecture and that some functions could be abnormal across so many of them is intriguing," said Thomas Insel, MD, director of the National Institute of Mental Health, who wasn't involved in the study but is familiar with its contents.

The researchers drew on component studies that have been around for some time, said Insel. But these studies tended to focus on one or another psychiatric disorder in isolation, whereas the Stanford investigators "have stepped back from the trees to look at the forest and see a pattern in that forest that wasn't apparent when you just look at the trees," Insel said.

"In many of these published studies we reviewed, researchers have tended to interpret their biological findings in terms of the one disorder they're focusing on," said Amit Erkin, MD, PhD, an assistant professor of psychiatry and behavioral sciences at Stanford and the study's senior author. Lead authorship is shared by Madeleine Goodkind, PhD, a postdoctoral scholar in Erkin's group, and Simon Eickhoff, DrMed, a professor of clinical neuroscience and medical psychology at Heinrich-Heine University Düsseldorf.

Similar gray-matter loss

Despite experienced clinicians' intuitive grasp of the blurred lines separating diverse psychiatric conditions, there's nonetheless often an assumption that these disorders, traditionally classified on the basis of predominant symptoms, are discrete in reality, noted Erkin, who is also an investigator at the Sierra-Pacific Mental Illness Research and Clinical Center at the Veterans Affairs Palo Alto Health Care System. "We tried to ask a basic question that hasn't been asked before: Is there any common biological basis for mental illness?"

To address that question, he and his colleagues pooled data from 193 separate studies containing, in all, magnetic-resonance images of the brains of 7,381 patients falling into six diagnostic categories: schizophrenia, bipolar disorder, major depression, addiction, obsessive-compulsive disorder and a cluster of related anxiety disorders.
A single stroke doubles a person’s risk of developing dementia over the following decade, even when that person’s mental ability is initially unaffected. Why this delayed deterioration occurs has been a mystery. Now, School of Medicine investigators think they have discovered a major reason for it.

In experiments using both mouse models of stroke and brain-tissue samples from patients, they linked the delayed onset of post-stroke dementia to the persistent presence, in the brain, of specialized immune cells that shouldn’t be there at all.

The discovery could potentially translate into ways of identifying people at high risk for dementia, allowing physicians to act before it is time to try to stave off the disease. Drugs that can disable these immune cells are also available.

At roughly 800,000 new cases per year, stroke is the second-biggest cause of serious long-term disability in the United States, generating $74 billion annually in treatment and caretaking costs. Of the 7 million living stroke survivors, one-in-three suffers from dementia, or will.

In a study published Feb. 4 in *The Journal of Neuroscience*, a team led by Marion Buckwalter, MD, PhD, assistant professor of neurology and of neurosurgery; and how long they lived after being diagnosed. The data allowed the researchers to track whether patients received care as recommended by the NCCN’s Clinical Practice Guidelines in Oncology.

The other data was from the California Office of Statewide Health Planning and Development. It contained discharge information, including patients’ additional medical problems and treatments received while in the hospital. The office also provides information about all California hospitals, including whether a patient was treated in an integrated or a non-integrated system. The results also support policies that drive the development of integrated health-care models as envisioned by the Affordable Care Act.

With health-care reform, millions more patients are entering the health-care system, and we’re going to need to become more integrated in order to meet the demand. We’re going to need to work more closely together, de- crease variations in care and standardize what we do,” said Rhoads.

The study was funded by the National Cancer Institute and a Harold Amos Medical Faculty Development Award from the Robert Wood Johnson Foundation.

Information about Stanford’s Department of Sur gery, which also supported the work, is available at sur gery.stanford.edu.

Lisa Marie Potter is a science-writing intern for the medical school’s Office of Communication & Public Affairs.

**Immune cells tied to delayed onset of post-stroke dementia**

**By Bruce Goldman**

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**By Lisa Marie Potter**

For the past two decades, the National Cancer In stitute has documented a persistent racial disparity in colon cancer survival rates in the United States. African-American patients have consistently had lower survival rates when compared with white patients, despite a nationwide decline in colon cancer deaths over time.

Now, a study by researchers at the School of Medi cine shows that more equitable distribution of evidence- based care can close this gap. Furthermore, the investi gators found that the evidence-based care was deliv ered at higher rates within integrated health-care orga nizations — those in which one organization provides all services, including health-care services, hospital care and insurance. The study reports that five-year death rates were lower for all colon cancer patients treated in an integrated health-care system, and the differences in survival by race were eliminated.

The study’s findings, published online Jan. 26 in the *Journal of the National Cancer Institute*, support the idea that providing equitable, high-quality, evidence-based care is a powerful tool in eliminating cancer-treatment disparities.

“It’s easier to do the right thing when you have the system-level support to do so.”

StudY: INtegrated care increased colon-cancer survival rates

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Stroke
continued from page 2

other types of immune cells, B cells are virtually nonexistent in the brain, with the exception of those whose outermost raptures are mostly impervious to the cells and large molecules (like antibodies) freely circulating elsewhere. But the blood-brain barrier is not entirely unreachable and is rendered much more permeable upon brain injury.

Two small reports from the last decade mentioned the puzzling presence of substantial numbers of immune cells in about 15 percent of human brains of people who had suffered strokes. This led Buckwalter to look more closely at the phenomenon.

Buckwalter is a team leader of Stanford’s Stroke Collaborative Action Network, which is part of the Stanford Neurosciences Institute and coordinates stroke research efforts throughout the university. She was intrigued by those findings and coordinated with scientists from the National Institutes of Health. Other Stanford researchers who participated in this study were researchers Jullet Han and Lisa and Sandra Jurado, PhD; and life science associate professor Seth Ammerman and infant health.”

Why pediatrics academy is troubled by legal pot

Four states and the District of Columbia have legalized the use of recreational marijuana, and 23 others recognize the medical use of marijuana. As the social and political climates shift, the American Academy of Pediatrics has reiterated that drug laws affect children as well as adults, and issued a new position statement on marijuana Jan. 26.

The lead author of the academy’s statement is Seth Ammerman, MD, clinical professor of pediatrics at the School of Medicine and medical director of the Adolescent Health Van operated by Lucile Packard Children’s Hospital Stanford. He said the position statement reiterates 10 recommendations that address one fundamental issue: How can we help keep our youth healthy.

Ammerman discussed the academy’s stance on marijuana with science writer Erin Digita.
Researchers use big data to identify patients at risk of high-cholesterol disorder

By Tracie White

School of Medicine researchers have announced the start of a new project designed to identify patients who may have a genetic disease that causes a deadly buildup of cholesterol in their arteries.

Using big data and software that can learn to recognize patterns, researchers will comb through electronic medical records to identify patients at risk of familial hypercholesterolemia, which often goes undiagnosed until a heart attack strikes.

This disorder certainly leads to premature death in thousands of Americans each year,” said Josh Knowles, MD, PhD, assistant professor of bioinformatics, and Ken Mahaffey, MD, professor of cardiovascular medicine, who will lead the effort with Nigam Shah, PhD, assistant professor of bioinformatics, and Kevin Fenton, MD, assistant professor of cardiovascular medicine.

By Krista Conger

In May of 1989, a new building opened its doors on the School of Medicine campus, and a grand experiment began.

The Beckman Center for Molecular and Genetic Medicine brought together researchers from across the school to exchange ideas and work together to integrate the practices of basic science with clinical medicine.

The Beckman Center for Molecular and Genetic Medicine, which opened in 1989, brings together researchers to exchange ideas and work together to integrate the practices of basic science with clinical medicine.

By Barry Starr, PhD, director of outreach activities for the Beckman Center, the Beckman Center at the Tech helped construct one of the museum’s permanent exhibitions, called “Genetics: Technology With a Twist.”

The program trains graduate students and postdoctoral scholars to work as docents who answer questions and lead hands-on activities, such as DNA extraction.

“I teach kids about DNA,” said Miguel Mata, PhD, professor of molecular and cellular physiology, who may have a genetic disease that causes a deadly buildup of cholesterol in their arteries. (Spoiler: Humans have fewer genes than amoebas.) The genomics exhibit is geared toward an older audience, but the docents are ready to answer questions from visitors of all ages.

“Genomics: Unlocking Life’s Code” opened Jan. 22 and runs through April 27. For more information about the exhibit, visit http://unlockinglifecode.org. The Tech Museum is open daily from 10 a.m. to 5 p.m.

Kimberlee D’Ardenne is a science-writing intern for the medical school’s Office of Communication & Public Affairs.

Beckman Center celebrates 25 years with symposium, ‘Innovation in the Biosphere’

The Beckman Center for Molecular and Genetic Medicine is funded by Amgen Inc., a bio-technology firm, and the American Heart Association. Researchers will use electronic medical records, stripped of personal patient identification, from Stanford Health Care and Stanford Children’s Health to conduct the research. They will report their findings to the patients’ personal physicians, who can encourage screening and therapy for those found to be at high risk for the disorder.

Using previous research methods pioneered by Shah, the project involves “teaching” a computer how to recognize a pattern in the electronic records of patients who have been diagnosed with the disorder. The computer is then instructed to analyze all patient records in the system for signs of the pattern.

Machine learning, in which computer algorithms learn to recognize patterns within data, is widely used by Internet businesses such as Amazon and Netflix to improve customer experience, get information about trends, identify likes and dislikes and target advertisements, Knowles said.

“These techniques have not been widely applied in medicine, but we believe that they offer the potential to transform health care, particularly with the increased reliance on electronic health records,” he said.

The general approach we’ll be pioneering has broad applicability in other arenas. Our algorithms will be broadly applicable to several different electronic health record platforms and the principles can be applied to other conditions.™

Beckman Center for Molecular and Genetic Medicine, which opened in 1989, brings together researchers to exchange ideas and work together to integrate the practices of basic science with clinical medicine.
Telomere extension turns back aging clock in cultured human cells

By Krista Conger

A new procedure can quickly and efficiently increase the length of human telomeres, the protective caps on the ends of chromosomes that are linked to aging and disease, according to scientists at the Stanford School of Medicine.

Treated cells behave as if they are much younger than untreated cells, multiplying with abandon in the laboratory dish rather than shrinking or dying. For the first time, the use of a modified type of RNA, will improve the ability of researchers to generate large numbers of cells for study or drug development, the scientists say. Skin cells with telomeres lengthened by the procedure divided many more times than untreated cells. The research may point to new ways to treat diseases caused by shortened telomeres.

Telomeres are the protective caps on the ends of the strands of DNA called chromosomes, which house our genes. In young humans, telomeres are about 8,000-10,000 nucleotides long. They shorten with each cell division, however, and when they reach a critical length the cell stops dividing or dies. This internal “clock” makes it difficult to keep most cells growing in a laboratory for more than a few cell doublings.

‘Turning back the internal clock’

“Now we have a way to lengthen human telomeres by as much as 1,000 nucleotides, turning back the internal clock in these cells by the equivalent of many years of human life,” said Helen Blau, PhD, professor of bioengineering and medicine at Stanford and director of the university’s Baxter Laboratory for Stem Cell Biology.

The newly developed technique has “great advances to be made in the near future. I think there’s a way to lengthen telomeres in cultured human muscle and skin cells. A 1,000-nucleotide addition represents a more than 10 percent increase in the length of the telomeres. These cells divided many more times in culture than did untreated cells: about 28 more times for the skin cells, and about three more times for the muscle cells.

“We were surprised and pleased that modified TERT mRNA worked, because TERT is highly regulated and must bind to another component of telomerase,” said Ramunas. “Previous attempts to deliver mRNA-encoding TERT caused an immune response against telomerase, which could be deleterious. In contrast, our technique is nonimmunogenic. Existing transient methods of extending telomeres act slowly, whereas our method works over just a few days to re-teleomere shortening that occurs over more than a decade of normal aging. This suggests that a treatment using our method could be brief and infrequent.”

Potential uses for therapy

“This new approach paves the way toward preventing or treating diseases of aging,” said Blau. “There are also applications involving genetic diseases associated with telomere shortening that could benefit from such a potential treatment.”

Blau and her colleagues became interested in telomeres when previous work in her lab showed that the muscle stem cells of boys with Duchenne muscular dystrophy had telomeres that were much shorter than those of boys without the disease. This finding not only has implications for understanding how the cells function — or don’t function — in making new muscle, but it also helps explain the limited ability to grow afro- cells in the laboratory for study.

The researchers are now testing their new technique in other types of cells.

“This study is a first step toward the development of telomere extension to improve cell therapies and to possibly treat disorders of accelerated aging in humans,” said John Cooke, MD, PhD, a co-author of the study, formerly was a professor of cardiovascular medicine at Stanford. He is now chair of cardiovascular sciences at the Houston Methodist Research Institute.

“We’re working to understand more about the use of this technology and how we can overcome those differences to allow this approach to be more universally useful,” said Blau, who also is a member of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

“One day it may be possible to target muscle stem cells in a patient with Duchenne muscular dystrophy, for example, to extend their telomeres. There are also implications for treating conditions of aging, such as diabetes and heart disease. This has really opened the doors for us to consider all types of potential uses of this therapy.”

Other Stanford co-authors of the paper are postdoctoral scholars Jennifer Brady, PhD, and Moritz Brandt, MD; senior research scientist Stéphane Corbel, PhD; research associate Colin Holbrook; and Juan Santiago, PhD, professor of mechanical engineering.

The work was supported by the National Institutes of Health, Germany’s Federal Ministry of Education and Research, Stanford Bio-X and the Baxter Foundation.

Ramunas, Yakubov, Cooke and Blau are inventors on patents for the use of modified TERT RNA for therapy.

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

Greenberg helped steer U.S. - India effort that led to vaccine

By Ruthann Richter

During his recent three-day visit in January to India, President Barack Obama joined a joint statement with Indian Prime Minister Narendra Modi praising the “highly successful collaboration” that led to the availability of a newly developed rotavirus vaccine, which is expected to save 80,000 children in India alone.

The vaccine was developed with support from the India-U.S. Vaccine Action Program, co-chaired since 2009 by Harry Greenberg, MD, senior associate dean for research at the Stanford School of Medicine. Greenberg also is professor of gastroenterology and infectious diseases at the Institute.

Greenberg said in a less-developed time ever that a new vaccine was developed in a relatively long time. “This greatly increases the number of children who can be immunized,” said Blau, who also is professor of bioengineering and medicine.

The vaccine is a “very transformative innovation,” according to scientists around the world, and it has now potential for great change, Stanford Bio-X and the Baxter Foundation.

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Using Google Glass

Contracting with Google Glass, Augmedix provides the much-publicized Internet-connected headgear, which looks and feels like a pair of eyeglasses, to doctors on a monthly subscription basis. Physicians wear the headgear during appointments with patients and capture data and images to instantly access a patient’s electronic medical records. A thumbnail-sized screen appears in the corner of the right eye of the device, which also has a camera and a microphone. The patient-doctor conversation is live-streamed to Augmedix where, with a combination of software and human support, notes are created and entered into the patient’s electronic medical records according to the doctor’s preferences, Tran said. When the doctor’s visit is complete, so is the record-keeping.

“The whole goal is to remove the hassle of paperwork, of data management,” said Kim. “We do this by giving them Google Glass. When they wear it they can stream the conversation directly to our service, and it gets translated into their electronic medical records.”

According to Tran, physicians who use the service have been able to reduce the number of hours spent record-keeping from an average of 17 a week down to just two — or even fewer. “It literally changes the lives of the doctors we work with,” he said. “They’re getting back 15 hours a week.”

Using Google Glass

Kevin Limostatin was identified by vir-

The metabolic dance

Insulin is a key player in the complicated metabolism of all organisms. Its importance can hardly be overstated. After a meal, animals and humans produce insulin in response to the rise in blood sugars as a meal is digested. This insulin stimulates the storage of circulating sugars into muscle and fat tissue as well as the suppression of new insulin production. Other metabolic processes, including smooth muscle contraction, are also affected by insulin levels, which can directly affect insulin production.

But exactly when is still up in the air. “It’s a very important molecule,” said Kim. “We believe it’s likely that the ‘aha’ moment that we found is very similar to the way we think about things in our environment. Finally, they were able to connect what they saw in the lab to a naturally occurring mutation in humans.”

“We found a variant of this hormone that is mutated in a human fam-

Snyder awarded $7.1 million from national genome institute

Michael Snyder, PhD, has been awarded a three-year, $7.1 million grant from the National Human Genome Research Institute to study how epigenetic gene expressions control the maturation of skin cells. Snyder’s work may aid in the understanding of autoimmune diseases and skin disorders.

The award is one of five granted as part of the newly launched Genomi-

Continued from page 1

“Snyder is the Stanford W. Ascherman, MD, FACS, Professor in Genetics and chair of the Genetics Department. He is also the director of Stanford’s Center for Genomics and Personalized Medicine. Other grant recipients intend to study biological processes involved in inflammation and pathogen response.

Insulin

continued from page 1

The metabolic dance

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Vaccine
continued from page 1

tions more likely to obtain desired results.

The Stanford Human Systems Immunology Center will draw upon a repertoire of technologies, many of which have been pioneered at Stanford, to provide a detailed profile of the human immune response. Seed grants will be made available to Stanford faculty, as well as investigators from other institutions, in order to fuel innovations in immunology and vaccine-related efforts.

Davis, the center's principal investigator, said animal models of vaccines have not been successful in most cases, as multiple vaccine candidates showed to work in mice and nonhuman primates have failed in human trials.

The need for new approaches

“What we need is a new generation of vaccines and new approaches to vaccination,” said Davis, who is the Burton and Marion Avery Professor of Immunology and director of the Stanford Institute for Immunity, Transplantation and Infectious Diseases. “This will help sustain the understanding of the human immune response and clearer predictions about vaccine efficacy and safety.”

Davis will be joined in the effort by Holden Maechler, PhD, associate professor of molecular and integrative physiology, and director of the Human Immune Monitoring Center; Garry Nolan, the Rachford and Carlota A. Harris Professor, also in the Department of Microbiology and Immunology; Arul Murte, MD, PhD, associate professor of pediatrics and of genetics; Yvonne Maldonado, MD, professor of pediatrics and of obstetrics and gynecology; and Karla Kirkeg- aard, PhD, the Violetta L. Horton Professor and professor of genetics; Peter Kim, PhD, the Virginia and Alfred H. Murad Jr. Professor of Chemistry; Thomas Baer, PhD, executive director of the Stanford Photonics Research Center; and other faculty.

The researchers also plan to analyze why some people are able to effectively fight off pathogens, while others remain vulnerable. For instance, many millions of people are carriers of the tuberculosis bacteria, yet fewer than 10 percent develop active disease.

“This grant will provide crucial support to Stanford’s world-class scientists as they collaborate with investigators around the globe to assess vaccines against some of the most formidable diseases of our time,” said Lloyd Minor, MD, dean of the School of Medicine. “The Stanford Human Systems Immunology Center will help the most promising vaccine candidates to move quickly and efficiently from the lab to the front lines of treatment, impacting countless lives.”

“We are pleased to make this grant, which is all about enabling collaboration,” said Chris Wilson, Ph.D., director of the Bill & Melinda Gates Foundation. “It will enable vaccinologists to take advantage of the state-of-the-art technologies that Stanford has developed to monitor the human immune response and allow Stanford investigators to collaborate to help solve one of the greatest challenges we face when trying to harness the power of the immune system to provide protection for those in the developing world.”

Stanford has a long track record in immunology. In 1970, the late professor Leonard Herzenberg, PhD, introduced fluorescence-activated cell sorting technology, an instrumentational technique that is now a mainstay in labs around the world. In the last decade, Stanford scientists have developed or refined a host of other sophisticated tools that are transforming the ability to understand immune responses in humans at a deep level. These include technologies that can rapidly analyze individual cells and tools that can provide a detailed portrait of the human immune system, with all of its many components.

“We hope our work will have a profound effect on our ability to develop new vaccines,” said Davis, who is also an investigator at the Howard Hughes Medical Institute.

Brain
continued from page 1

orders. Comparing the images with those from 11 healthy control subjects, the research team identified three separate brain structures, several centimeters apart from one another, with a diminished signal. (see Figure.) The brain tissue that serves to process information. These structures — the left and right anterior insula and the dorsal anterior cingulate — are known to be parts of a larger network in the brain whose component parts tend to fire in syn- chrony. This network is associated with higher-level executive functions such as concentrating in the face of distractions, multitasking or task-switching, planning and decision-making, and inhibition of counterproductive impulses.

Gray matter loss in the three brain structures was similar across patients with...
In 1979, seventh-grader Lloyd Minor was bused from his white Little Rock, Arkansas, neighborhood to attend one of the city's black schools as part of urban desegregation efforts of the era. What he saw there stuck in his memory: Plaster peered off the walls, and the library had only about 100 books.

“What I had been told was separate but equal was certainly separate, but in no way was it equal,” Minor said. “That caused me then to see that diversity is a mandate — isolating the first year, she said. By contrast, about 40 percent of the workforce. The company recently captured headlines by pledging $500 million over three years to recruit and retain more minorities and women.

“Why aren’t we better?”

“We’ve spent the last decade building capability,” Hudnell explained. “Then, we stepped back and said, ‘Why aren’t we better than what’s been written books.”

The key is to set goals to boost diversity and hold everyone accountable, she said. Now, Intel is committed to teaching market representation across its work-force by 2020. Hudnell admitted she isn’t quite sure how that’s going to happen, but she’s confident it will. “It’s time to use our capability and lead.”

And in that regard, she believes Stanford’s School of Medicine has an advantage. “I think, quite frankly, you are incredibly blessed to have a leader who truly gets it,” Hudnell said.

The medical profession is in a much better place than engineering and technology fields, she said, and she challenged those in the audience to think about what “you’re going to do with this phenomenal capability that you’re sitting on.”

One step is to install institutional safe-guards to combat bias, Hudnell said. The biases won’t be eliminated — they thrive in an atmosphere driven by high standards and right deadlines — conditions that are present at both Intel and Stanford, she said. But by offering training and fostering transparency and oversight, bias can be minimized.

According to Hudnell, another key ingre-dient of workplace diversity is encouraging a healthy work-life balance. Although many programs to support child care and personal wellness are in place at Intel and other technology compa-nies, she said the next step is to ensure workloads are appropriate.

Hudnell noted that she hopes to work with Minor in the future on cooperative efforts to build diversity. 

The next lecture in this series will feature Vivek Wadhwa, a fellow at Stanford’s Center for Corporate Governance. Wadhwa will speak at noon Feb. 20 at the Li Ka Shing Center for Learning and Knowledge.