INSIDE STANFORD MEDICINE

Volume 7, No. 22 ■ December 14, 2015 ■ Published by the Office of Communication & Public Affairs

A 3,200-year-old mummy took a day trip to the School of Medicine for a CT scan.
Page 4

Neuroscience center to open for patient care

By Sara Wykes

Chris Bjornson, diagnosed with multiple sclerosis in 2008, does not have good memories of getting to his medical appointments at Stanford Health Care. The damage done by his disease to his muscle control and coordination means he must walk as if he might fall with his next step — and he has.

Crowded or narrow hallways, changes from carpet to tile, and long distances between one place and another are daily threats to his stability. "I had to mentally prepare myself to go to appointments to be ready for those challenges," Bjornson said, "but I didn't think there was anything I could do about it."

Those physical barriers to his care and the stress they added are now a thing of the past. On Dec. 10, a ribbon-cutting ceremony was held to celebrate the completion of the Neuroscience Health Center, which will open to patients in January.

The building is tuned to the needs of people with neurological conditions or injuries such as brain tumors, movement disorders, brain aneurysms, spine deterioration, Parkinson's disease and memory disorders. Bjornson, a member of the Patient and Family Advisory Council for the center, was happy to be only figuratively bowled over as he explored the outpatient center for the first time. "It's astounding," he said. "The world doesn't make any exceptions for people whose movements or thinking are affected by neurological disorders. To have this building that's been made specifically for us is astounding."

"We had a vision," said Alison Kerr, vice president for operations at Stanford Health Care and one of the new center's project leaders. "Five years ago, our neurology, neurosciences and interventional neuroradiology clinicians met with our counterparts in the School of Medicine to establish a partnership to build this center."

NORBERT VON DER GROEBEN

Amir Dan Rubin, president and CEO of Stanford Health Care, cuts the ceremonial ribbon Dec. 10 at an event celebrating the completion of the Neuroscience Health Center. He is joined by the School of Medicine Dean Lloyd Minor (far left), government officials and Stanford Medicine faculty and staff.

From the ground up

The project had two goals: Build a center that would exemplify what neurological patient care should look like and what scientific and clinical collaboration among specialists in 21 neurological subspecialties could be. They all knew it could only be done from the ground up.

"At Stanford Medicine, we are committed to working across boundaries to provide preventive, personalized and patient-centered care for our patients," said Lloyd Minor, MD, dean of the School of Medicine. "Through the Stanford Neuroscience Health Center, we are leading the biomedical revolution in precision health by providing our neuroscience patients with individualized care that is focused on wellness and integrates the most technologically advanced equipment with groundbreaking discovery."

The 92,000-square-foot, five-story building's assets are considerable: a site at the cor-
See NEUROSCIENCE, page 6

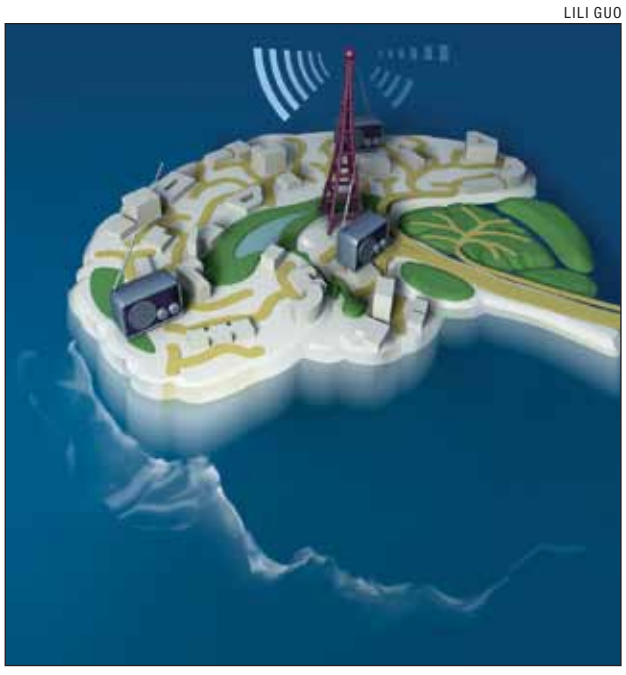
Study: Nerve-cell firing rates affect alertness

By Bruce Goldman

Adjusting a specific deep-brain circuit's firing frequency immediately and dramatically alters rats' forebrain activity and alertness levels, School of Medicine investigators have shown.

The findings, published online Dec. 10 in *eLife*, hold direct implications for an increasingly widespread therapeutic approach called deep-brain stimulation. They point to DBS's potential for restoring consciousness in minimally conscious patients and countering other cases of impaired consciousness. The findings also highlight the importance of determining optimal stimulation frequencies for DBS devices used across a wide range of brain disorders and demonstrate a method for making those determinations.

LILI GUO



The research suggests that a brain structure can be like a radio whose different stations, playing different kinds of music, variously attract or repel different "listening audiences."

The research suggests that a brain structure can be like a radio whose different stations, operating at different frequencies and playing different kinds of music, variously attract or repel different "listening audiences."

DBS involves the insertion of an electrical-signaling device into a specific area of the brain. It has provided therapeutic benefits to patients with disorders ranging from Parkinson's disease and essential tremor to major depression and obsessive-compulsive disorder.

"The methods we employed for tracking the circuitry of arousal regulation in the brain can guide DBS research on all of these disorders, and others," said the study's senior author, Jin Hyung Lee, PhD, assistant professor of neurology, of neurosurgery and of bioengineering at Stanford. "The brain structures that we showed to be critical in regulating arousal, and the connections between them, are virtually the same in rats and humans, so we have high hopes of seeing our findings, as well as our methods, translated into clinical trials."

Lead authorship is shared by postdoctoral scholar Hyun Joo Lee, PhD, and graduate students Jia Liu, Andrew Weitz and Zhongnan Fang.

Another of the study's coauthors is Nicholas Schiff, MD, professor of neurology and neuroscience at Weill Cornell Medical College in New York City. In a case study published in 2007, Schiff and his colleagues demonstrated that electrically stimulating the central portion of the thalamus — a deep-brain relay station routing inputs from the senses to myriad cognitive-processing centers throughout the cerebral cortex — could restore consciousness in a patient who'd been in a minimally conscious state for six years.

"But there was no way to know how it worked," said Lee. "Electrical stimulation nonselectively triggers firing in all kinds of nerve cells
See THALAMUS, page 7

Common treatment for prostate cancer appears to double Alzheimer's risk

By Jennie Dusheck

A review of the electronic medical records of thousands of prostate cancer patients at two major medical institutions revealed a nearly two-fold increase in the rate of Alzheimer's disease diagnosis among those treated with androgen deprivation therapy.

Nigam Shah

The study, by researchers at the Stanford School of Medicine and the University of Pennsylvania Perelman School of Medicine, demonstrates emerging techniques for extracting biomedical data from ordinary patient medical records.

The paper was published online Dec. 7 in the *Journal of Clinical Oncology*. Nigam Shah, MBBS, PhD, associate professor of biomedical informatics research at Stanford, is the senior author. The lead author, Kevin Nead, MD, is a resident at the University of Pennsylvania who got his medical degree at Stanford.

Because testosterone can promote the growth of prostate tumors, clinicians have used androgen deprivation therapy to lower testosterone and other androgens in prostate cancer patients since the 1940s. In the United States, about a half-million men currently receive ADT as a treatment for prostate cancer.

The researchers scanned the records of 1.8 million patients from Stanford Health Care, in Palo Alto, and, through a
See ANDROGEN, page 6

■ OBITUARY

Herbert Schwartz, former chair of pediatrics, dies at 89

By Erin Digitale

Herbert Schwartz, MD, professor emeritus and former chair of the Department of Pediatrics at the School of Medicine, died Nov. 13. He was 89.

Schwartz, who helped build the pediatric hematology and oncology teams at Stanford starting in the 1960s, was known by his colleagues as a caring, dedicated physician and a respected mentor and scientist. He served as acting chair of the Department of Pediatrics from 1969-70 and as chair from 1970-71.

"He was an excellent teacher, and was very devoted to the house staff and medical students," said Philip Sunshine, MD, professor emeritus of pediatrics, who worked with Schwartz for many years. "He was a really great role model for them." Schwartz was a frequent sounding board for his colleagues' research ideas because of his broad knowledge of the medical literature, Sunshine added.

Herbert Schwartz

Schwartz was a hematologist who specialized in blood disorders and conducted research on hemoglobin, the oxygen-carrying protein in blood. He studied how hemoglobin is synthesized, discovered an abnormal form present in patients with some hemolytic anemias, and examined how changes in maternal hemoglobin in diabetic women affect the fetus during pregnancy.

"He was a kind, gentleman scholar. He liked to talk about all things science, and he was able to interest you in things he found interesting," said Hendrik Vreman, PhD, senior research scientist in pediatrics. One day in 1982, Schwartz left a note on an intriguing *Science* paper about neonatal jaundice for David Stevenson, MD, the principal investigator of the lab where Vreman still works. The ideas in that paper inspired a series of studies that Stevenson, professor of pediatrics, and Vreman are still conducting. "My life has never been the same," said Vreman. "He really affected my career tremendously. That career has given me a lot of pleasure, and it was all due to Herb."

The value of physical contact

"He was an excellent clinical hematologist, warm, compassionate and well-liked by all the patients he cared for," said Bert Glader, MD, professor of pediatric hematology-oncology, who was recruited to Stanford by Schwartz in 1977. "I learned a great deal of hematology from him, particularly about the synthesis and function of hemoglobin. However, my most important memory of Herb is his advice for helping patients feel comfortable in a busy hospital environment. He said, 'Touch your patient every day.' As hospital medicine becomes increasingly technology-focused, I think his wisdom about the value of human contact is more important than ever."

Schwartz was born May 8, 1926, in New Haven, Connecticut. He joined the Navy during World War II and then attended college and medical school, earning his medical degree at the State University of New York in Brooklyn in 1952. He first came to Stanford as a medical resident in 1954-55, spent five years as a research fellow at the University of Utah, and returned to Stanford as a faculty member in 1960.

While in Utah, Schwartz met an art student named Carolyn Jex. They married in 1957, had a son, Michael, and twin daughters, Rebecca and Sara, and lived for 47 years in Palo Alto. Schwartz was known for riding his bicycle to work, favoring plaid shirts over white coats and playing tennis with a group of faculty led by Sunshine, who dubbed them the SWAT team, for Sunshine's Wednesday Afternoon Tennis. Schwartz also loved to play the cello and was enthusiastic about his wife's career as an artist.

"They had this really wonderful relationship," Sunshine said. "He was always so proud of her accomplishments."

Schwartz retired in 1991, after working with his colleagues in the Department of Pediatrics to plan and open Lucile Packard Children's Hospital Stanford, which welcomed its first patients that year. He and his wife moved to Gardnerville, Nevada, in 2007 to be closer to their son. Together, they took cruises all over the world, supported local orchestras, and enjoyed the company of their children and grandchildren. They were married for 56 years. She died in 2013.

He is survived by their three children: Michael Schwartz of Incline Village, Nevada; Rebecca Chamberlain of Solana Beach, California; and Sara Heller of Kentfield, California, who is a nurse coordinator at Stanford Children's Health in pediatric hematology/oncology. Schwartz is also survived by 10 grandchildren and three great-grandchildren.

Donations in his memory can be made to Lucile Packard Children's Hospital Stanford at www.supportlpch.org. ISM

Researchers identify new class of RNA tumor suppressors

By Krista Conger

A pair of RNA molecules originally thought to be no more than cellular housekeepers are deleted in over a quarter of common human cancers, according to researchers at the School of Medicine. Breast cancer patients whose tumors lack the RNA molecules have poorer survival rates than their peers.

The RNA molecules directly associate with and inhibit a well-known, cancer-associated protein called KRAS, the researchers found. In their absence, KRAS becomes hyperactive and issues continued signals to the cell to divide.

"This is the first time an RNA molecule in this class has been shown to act as a powerful tumor suppressor," said Paul Khavari, MD, PhD, professor and chair of dermatology at Stanford. "It does so by inhibiting the function of one of the most powerful cancer-causing proteins in the cell."

Khavari is the senior author of the study, which was published online Nov. 23 in *Nature Genetics*. The lead author is Zurab Siprashvili, PhD, a senior scientist at Stanford.

An oncogene is a gene that, when mutated, can cause cancer. The mutated gene creates a malfunctioning protein that encourages a cell to divide uncontrollably or enables it to sidestep the normal breakpoints that would halt cell division or launch a cellular suicide program to protect the organism.

The KRAS protein is a product of an oncogene. The protein sits on a cell's outer membrane and functions as an on-off switch to control cell division. Normally, it helps cells respond appropriately to external signals calling for cell growth. When mutated, however, it encourages the cell to undergo repeated rounds of cell division. KRAS mutation is an essential step in the development of nearly all human cancers.

Deadly deletions

The RNAs studied by the researchers are small, noncoding RNAs known as snoRNAs. Unlike the more familiar messenger RNA molecules that carry protein-making instructions from the DNA in the nucleus to the outer cellular machinery called ribosomes, noncoding RNAs fulfill other necessary cellular functions. SnoRNAs are known to help assemble the ribosomes themselves, for example. Siprashvili and his colleagues were interested in learning what role snoRNAs might play in the development of human cancers.

To do so, they compared 5,473 tumor genomes with the genomes obtained from surrounding normal tissue in 21 different types of cancer. In many ways, cancer cells represent biology's wild west. These cells divide rampantly in the absence of normal biological checkpoints, and, as a result, they mutate or even lose genes at much higher rate than normal. As errors accumulate in the genome, things go ever more haywire.

The researchers found that a pair of snoRNAs called SNORD50A/B had been deleted in 10 to 40 percent of tumors in 12 common human cancers, including skin, breast, ovarian, liver and lung. They also noted that breast cancer patients whose tumors had deleted SNORD50A/B, and skin cancer patients whose tumors made lower levels of the RNAs than normal tissue, were less likely than other similar patients to survive their disease.

Paul Khavari

"We were searching for areas of the genome that are highly abnormal in cancer cells," said Khavari, who is the Carl J. Herzog Professor of Dermatology. "We were very surprised to find SNORD50A/B so frequently deleted in so many different kinds of cancer. They are deleted as often as other very well-known tumor suppressor genes."

Because snoRNAs are best known for their role as housekeepers, it was surprising to find SNORD50A/B so directly implicated in human cancer. Khavari and his colleagues investigated to see if the RNAs were associated with any particular proteins in the cancer cells.

"Stunningly, we found that these RNAs associate with proteins in the RAS family, and specifically KRAS," Khavari said. "This is really last thing we would have expected. It was particularly surprising because my lab has been studying KRAS intensively for more than a decade, so it was quite a coincidence."

Goading cancer cells to divide

Siprashvili set out to find out more about the interaction between KRAS and SNORD50A/B. He found that when he deleted SNORD50A/B in human melanoma and lung cancer cells grown in the lab, the cells divided more quickly and displayed more cancerous traits than when SNORD50A/B was present.

Finally, they showed that when SNORD50A/B binds to KRAS, it inhibits the protein's ability to associate with an activating molecule called farnesyltransferase. Farnesyltransferase modifies the KRAS protein in such a way to allow it to travel to the cell's membrane to await external signals for growth and division.

"Normally, SNORD50A/B and farnesyltransferase work together to balance KRAS' function and allow it to respond appropriately to external signals," Khavari said. "When SNORD50A/B are missing, the balance is tilted toward KRAS hyperactivation."

In other words, when the genes for SNORD50A/B are lost from the genome, KRAS is free to goad the tumor cells to undergo repeated rounds of cell division.

Khavari pointed out that many pharmaceutical companies have been striving unsuccessfully to find a way to block farnesyltransferase's ability to activate KRAS. Understanding the role of the SNORD50A/B RNAs in this process could open new doors to blocking KRAS function in cancer.

The research was supported by the U.S. Veterans Administration's Office of Research and Development and by the National Institutes of Health.

Other Stanford-affiliated authors are former graduate student Dan Webster, PhD; research assistant Rajani Shenoy; graduate students Aparna Bhaduri and Yonglu Che; former postdoctoral scholars Alexander Ungewickell, MD, PhD, and Francesca Meschi, PhD; senior research associate Ross Flockhart, PhD; postdoctoral scholar Brian Zarnegar, PhD; technician Danielle Johnston; and professor of structural biology Joseph Puglisi, PhD.

Stanford's Department of Dermatology also supported the work. ISM

INSIDE STANFORD MEDICINE

Inside Stanford Medicine is published monthly in July and December and semi-monthly the rest of the year.

is produced by
Office of Communication & Public Affairs
Stanford University
School of Medicine
3172 Porter Drive
Palo Alto, CA 94304
Mail code 5471
(650) 723-6911
http://med.stanford.edu/news/

Paul Costello
Chief communications officer
Susan Ipaktchian
Director of print & Web communications
John Sanford
Editor
Robin Weiss
Graphic designer

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

STANFORD MEDICINE

OBITUARY

Spyros Andreopoulos, former news director, dies at 86

By Rosanne Spector

Spyros Andreopoulos, the director of Stanford Medicine's news and public affairs office for 30 years and a writer dedicated to educating the public about health care and biomedical research, died Nov. 20 at a nursing home in Menlo Park, California. He was 86.

Andreopoulos was known as a champion of openness in university communications. His advocacy of truthfulness and transparency in the School of Medicine's activities led some, including the dean at the time of his retirement, to call him "the conscience of the medical school." And while the school's leaders did not always heed Andreopoulos' characteristically blunt recommendations, many eventually came to see the wisdom of his advice.

Born in Athens, Greece, on Feb. 12, 1929, Andreopoulos learned English in German-occupied Salonica as a teenager, served as a communications liaison in Greece's air force during the Korean War, and studied journalism in the United States, where he married and remained. He worked in public relations and journalism, earning recognition among reporters and public-relations specialists as an unusually well-informed, honest and sometimes bold broker of medical news.

"In my experience, Spyros was one of the most competent, most helpful and most completely honest people in the public information world that I've encountered or dealt with," said longtime *San Francisco Chronicle* science reporter David Perlman in a 2009 interview. "You could always count on him to give you a straight answer and be totally forthcoming on matters of medical center policy. He was one of the very best in the business."

Though he was not a member of Stanford's faculty, Andreopoulos commanded the respect and attention of leaders in medicine at Stanford and beyond.

'Tell the story honestly'

"Over the years I was at Stanford, we had lots of episodes that weren't very pleasant," said David Korn, MD, a professor at Harvard University who was dean of Stanford's medical school from 1984-95, in a May 2010 interview. "Spyros would always say, 'We have to get that story out.'"

"Spyros believed very firmly that you can't hide things, and you shouldn't hide things, and if something happens at the university that is regrettable it's always best for the university to get out there first, tell the story honestly and put its spin on it — rather than let it trickle out and leave it to the media to report it in a way that's incomplete and, more than that, with the spin that the media chooses to put on it," Korn said.

Andreopoulos served as spokesman for the medical school and Stanford Hospital, director of the medical center's news office and adviser to the organizations' leaders. He also was a prolific and insightful writer himself.

"I have been brought up short more than once by things you've written that I thought put a new ethical stance to something that I had felt I understood but turned out I didn't understand very well," said biology professor Donald Kennedy, PhD, in 1993, at Andreopoulos' retirement party at the Stanford Faculty Club. Kennedy was Stanford's president from 1980-92.

Among the issues Andreopoulos took up over the years: the dangers of conflicts of interest in medical research, the strengths of single-payer health coverage, and methods for avoiding hype in reporting biomedical research.

Questioning authority

Andreopoulos played the diplomat, but only up to a point. He knew his opinions ruffled feathers, but that didn't stop him from pushing for what he thought was right. Though he looked the sober gentleman — unfailingly polite and, even in his college days, dressing in a neat jacket and tie and a dapper, flat cap — deep down he was a fighter.

"I respect authority," said Andreopoulos in an interview in 2010. "But I don't believe that authority cannot be questioned."

Considering his background, that's no surprise. His father, George Andreopoulos, carried out World War II resistance operations in Greece under the eye of the occupying German soldiers, moving Jewish families out of harm's way. For two years during the war, the Andreopoulos family took in a Jewish woman and her daughter under the pretense they were cousins.

During the war, which came to Greece in 1940, Andreopoulos went to high school and took English lessons. Among his classmates were several German officers, who had been encouraged to learn English before joining Field Marshal Erwin Rommel's Afrika Korps.

Greece was liberated by Britain in 1944, and in 1948-49, Andreopoulos studied at the University of Athens, "where I majored in chemical engineering that my father wanted but I did not," he said. His studies were cut off when the Royal Hellenic Air Force drafted him for two years of service in Korea, a blessing in disguise, he said.

Andreopoulos got his first experiences as a diplomat as the spokesman for a squadron of seven Douglas C-47 transport planes contributed by Greece to the U.S. effort in Korea. Because C-47s have a short range, they had many stops along the way to the base in Japan: in Cyprus, Saudi Arabia, Pakistan, India, Thailand, Burma, Vietnam and the Philippines. Andreopoulos flew in the plane leading the formation. "In each of these countries, some of which had governments that did not approve of the war in Korea, I did the diplomatic work," he said. While serving, he also had his first journalism experiences, recording interviews with the troops for Radio Athens.

Spyros Andreopoulos

Mixing military, English skills

Though he was trained in flight control, his knowledge of English led to his first job in communications. "Because I was one of the few English-speaking Greeks, my job in Korea and Japan was that of a liaison," he said. "Our squadron was integrated with the U.S. Air Force's 21st Troop Carrier Squadron and operated as one unit. Because we changed bases often, we became known as the 'Kyushu Gypsies.' My job was to keep communications between the Gypsies smooth." Kyushu is one of the islands of Japan.

After the war, Andreopoulos returned to Greece and worked for the United States Information Agency, helping produce a series of films on the accomplishments of the Marshall Plan in Greece. In 1953, he went to Kansas State University to learn about agriculture to prepare for writing the scripts for a film series teaching Greek farmers to use modern methods. The project was canceled the next year, but Andreopoulos was able to stay in the United States and enrolled in Wichita University, now Wichita State University, to study journalism with the help of a $2,000 scholarship, plus free room and board. "This was a lot of money in 1954," he said.

> "You could always count on him to give you a straight answer."

In 1955, while still a student in Wichita, he joined the *Wichita Beacon* newspaper as a reporter covering the education and science beats, and two years later he became assistant editorial page editor.

In 1959, the famous psychiatrist Karl Menninger, MD, asked Andreopoulos to join The Menninger Foundation in Topeka, Kansas, as assistant director of information services and editor of *The Menninger Quarterly.* He worked at the psychiatric clinic and school until a 1963 offer from Stanford lured him away.

Once at Stanford, Andreopoulos had plenty of administrative matters to write about — and plenty of news to get out. He wrote about tensions between the medical center and the city of Palo Alto, the creation of a virus in a test-tube, the first successful heart transplant in the United States and the Asilomar Conference on the safety of research using bioengineered materials. The attitude of the university's administration in those years suited him perfectly. "We had a carte blanche from Lyle Nelson, who was the director of public affairs at that time, to act almost independently, like a news organization and to cover the university fully, factually and to not worry about whether something we reported was negative," he recalled.

"The thinking was that in the long run, most of the news would be very positive. Occasionally there will be a negative story but by virtue of the fact that we were volunteering it ourselves and covering it ourselves, we diminished the possibility of it becoming a big scandal."

As director of Stanford's medical news office, Andreopoulos served as the official spokesman for the school and hospital, and also as editor of *Stanford M.D.* magazine and its successor, *Stanford Medicine,* which he founded. He became director emeritus in 1993.

Prolific writer

Other noteworthy Andreopoulos writings include the book *Aging of America & the Role of the Academic Health Center* (1988) and the article "The Unhealthy Alliance Between Academia and Corporate America" (2001) concerning the distorting influences of the commercialization of academic science on university research. He co-authored a medical novel, *Heart Beat*, (1978). *Primary Care: Where Medicine Fails*, which he edited, received the Best Book Award from the American Medical Writers Association in 1975, and *National Health Insurance: Can We Learn from Canada?*, which he edited, was named Book of the Year by the American Nurses Association in 1976.

He also edited and contributed to other books on socioeconomic aspects of health care.

As a member of the board of the Sun Valley Forum on National Health, a think tank cofounded in 1972 by the late Averill Harriman and based in Sun Valley, Idaho, Andreopoulos authored and published policy papers on a range of topics.

Beginning in 1995, he contributed more than 60 commentaries to the *San Francisco Chronicle*, *San Jose Mercury News* and other newspapers on topics ranging from medical education and research to drug company advertising, health-care policy issues and the uninsured.

He received several exceptional achievement awards from the Association of American Medical Colleges for "excellence in medical education public affairs," and on the year of his retirement, *Stanford Medicine* magazine received the Sibley Award for excellence from the Council for Advancement and Support of Education, the highest honor accorded to university magazines.

Andreopoulos served on the boards of the California Division of the American Cancer Society and the National Association of Science Writers. He was a member of the American Medical Writers Association and served as a consultant on public relations and communication to the National Cancer Institute, several academic medical centers, the Henry J. Kaiser Family Foundation, the Markey Charitable Trust and the Lucile and David Packard Foundation. In the early 1970s, he advised PBS and the National Science Foundation during the initial planning and launching of the *NOVA* television series.

'I stand by those words 100 percent'

When Andreopoulos retired from the medical school in 1993, Korn, who was the dean at the time, had a commemorative scroll prepared for him. It is now framed in the Stanford campus house where Andreopoulos lived for decades, and where his wife, Christiane, still resides. It reads: "A respected and loyal friend of Stanford, a man of the highest principles, you served as the conscience of the Medical Center, working with uncommon skill and probity to translate and disseminate scientific research, striving always to discern and communicate the truth. We salute your long and distinguished career."

Said Korn, nearly 20 years later: "I stand by those words 100 percent."

In addition to Christiane, who for many years taught French at Castilleja School, an all-girls middle and high school in Palo Alto, California, Andreopoulos is survived by a sister, Rena Michalopoulos, of Athens, Greece; daughter Sophie Fitch of San Carlos, California; and granddaughters Kelly Anne and Alison Fitch.

Memorial donations can be made to the Guttmacher Institute by calling (800) 355-0244 ext. 2237 or by visiting http://www.guttmacher.org. ISM

Egyptian mummy visits medical school for CT scan

By Jennie Dusheck

PHOTOS BY NORBERT VON DER GROEBEN

Clockwise from top: A 3,200-year-old Egyptian mummy arrives Nov. 24 at the School of Medicine. Terilyn Moore, a Siemens contractor, helps make sure the mummy is correctly lined up for scanning. Renée Dreyfus (foreground), a curator with the Fine Arts Museums of San Francisco; Jonathan Elias, director of the Akhmim Mummy Studies Consortium, and Kerstin Müller, an instructor of radiology at Stanford, collaborate with other specialists on the imaging project.

Thousands of years ago lived a woman in the Egyptian city of Asyut, on the west side of the Nile River Valley, 375 miles south of the Mediterranean city of Alexandria. Her true name is unknown, but today some call her Hatason.

Asyut was at the crossroads of several trade routes. It was rich in culture but, because of all those roads, vulnerable to attack, and therefore protected by well-armed soldiers. Asyut lay just below a constriction in the river that allowed Asyut officials to stop traders carrying cargo downstream to the cities of the north and extract tolls from them.

Asyut also lay at the north end of the infamous Darb el-Arba`īn, the Forty Days' Road, coming through the desert from Darfur; the 1,100-mile road was a major route for trading gold, ivory, spices, animals — and people. Until well into the 18th century, millions of slaves were forced to walk out of Africa on the Darb el-Arba`īn.

When Hatason died, about 3,200 years ago, someone took the time to mummify her. Her coffin depicts a woman in everyday clothes. But did her mummified remains originally belong in that coffin? Stanford Egyptologist Anne Austin explained, "When mummies came into the collections of most museums in the late 19th century and early 20th century, they were dated and sexed based on the coffin the mummy was found in. We now know that rampant reuse of coffins means these assumptions may be wrong."

Sometime in the 19th century, Hatason's mummified body was moved from its tomb and eventually shipped to foggy San Francisco, where she was put on display in Golden Gate Park as part of the California Mid-Winter International Exposition. In March 1895, her body was donated to the city's new de Young Museum. Since then, she has spent 35 years visiting the Rosicrucian Museum in San Jose, taken a yearlong trip to Hawaii and resided at the Legion of Honor, a San Francisco museum overlooking the Pacific Ocean.

Radiology appointment

On Nov. 24, Hatason took a day trip to Stanford's Department of Radiology to undergo a computed tomography scan that may tell Renée Dreyfus, a curator with the Fine Arts Museums of San Francisco, more about who Hatason was. Hatason arrived on campus in a white box at about 10 a.m., pursued by nearly a dozen camera-clicking communications staffers from the Fine Arts Museums and Stanford Medicine. As museum workers wheeled her through the doors of the Grant Building, an elderly bystander demanded to know what was in the box. When told, he frowned and walked away toward the rainy parking lot.

Hatason's first stop was the zeego imaging lab in a basement near Stanford Hospital. The lab isn't where you go to find out if you have a tumor; it's a research lab with a high-end CT scanner, managed by Kerstin Müller, PhD, an instructor of radiology at the medical school, who oversaw the imaging. She put on a full-coverage lead blouse and skirt, decorated with small printed skulls, that protected her from radiation from the scanner. A raft of experts from Stanford, the Fine Arts Museums of San Francisco and Siemens, which built the zeego scanner, worked seamlessly together to set up and scan Hatason.

The team gently removed Hatason from her box and lifted the small and delicate mummy, wrapped in bright white paper, onto the scanner. The zeego lab has imaged other mummies, including two mummified crocodiles. But the lab specializes in research on imaging the complex 3-D patterns traced by the arteries and veins of the body. When surgeons need to thread a catheter through a blood vessel, it's extraordinarily difficult to follow the exact path without detailed images. Earlier in November, researchers used the lab's CT scanner to test a new approach for imaging arteries in a live pig. The lab is also working on a technique for blocking the blood supply to tumors in the liver. But on Nov. 24, the giant machine focused on finding out more about Hatason.

So little is known about her that the museum still wasn't positive that she was a woman, or how ancient she was. Even her name is an invention. "This mummy is known historically as Hatason," said Jonathan Elias, PhD, director of the Akhmim Mummy Studies Consortium. "That is not her name. That is a corruption, we believe, of the name of a famous queen, Hatshepsut." Private collectors of the 1890s liked to think they were purchasing royal mummies. Salesman likely named the mummy Hatason to make her sound like a queen.

Was she the same age as the coffin she has been stored in? Or could it have been from an earlier or later period? As the scanner's long arms whirred and spun around the mummy, the roomful of radiology and mummy experts stared intently at the images coming up on several computer displays for clues about who she was. The shape of her skull and hips could reveal her sex, and the way she was wrapped and the presence of amulets might say something about her status.

Inside the skull

As the crowd in the room jammed together behind a protective wall, the scanning began at Hatason's head. When the first images of her skull appeared on the screen, Elias, who had flown all the way out from Pennsylvania to view the scans, expressed surprise. He pointed out that Hatason's brain was still inside her skull, but it was resting atop a pile of dark matter he said was probably sediment. "It's some form of material added into the brain case while the brain was left inside," he said. "We have not seen that particular pattern before."

> **"There are not that many mummies from this era that have been researched."**

The bones of her nose were intact, indicating that no one had even tried to remove her brain. Elias said the sediment was likely injected into her skull on purpose. But why? A thousand years later, he said, it would have been standard to remove the brain. In Hatason's time, mummy experts seemed to have been experimenting with preservation techniques.

No amulets appeared, just an obviously modern metal tack that may have been placed by some long-dead museum curator to hold the mummy's wrappings in place. After more than 3,000 years, nearly all of the mummy's organs, muscles and other tissues had vanished, and little held her bones together. Although the wrappings still outlined the shape of her body, down to the exact shape of her feet, the cast made by the wrappings was hollow except for her bones. Many had come loose and lay in jumbles — a hip bone in her former abdomen, foot bones in her thigh.

The bones of her pelvis had collapsed and could not reveal her sex, but Elias believed that her skull was clearly not that of a male. After some thought, he said, "a young adult, a woman." He and Dreyfus sat together for hours pointing to different clues on the screen in front of them, conferring and explaining things to those around them.

"What would convince you that the mummy is New Kingdom?" Müller asked Elias, referring to the period in Egypt between the 16th and 11th century B.C. The way the mummy was prepared, said Elias. "The fact that there was no excerebration [removal of the brain]. In mummies manufactured after a certain time, there is excerebration almost 100 percent of the time. But we have no excerebration," he said.

It will take some weeks to process the images, study them further and think about what they say about Hatason and the history of mummies generally, Elias said. "There are not that many mummies from this era that have been researched," he added. Soon though, a company that specializes in three-dimensional imaging and museum exhibits will work with the Legion of Honor on a special exhibit to display Hatason and a 3-D model of the mummy next spring. **ISM**

Researchers determine sleep gene linked to heart failure

By Lindzi Wessel

Researchers at the School of Medicine have identified a gene that, when working properly, appears to reduce the risk of heart failure and improve treatment outcomes, highlighting a possible target for the development of new drugs.

The gene codes for a protein that was first identified when a mutated form was shown to cause narcolepsy.

Caring for patients with heart failure costs the United States $40 billion a year, according to Euan Ashley, MRCP, DPhil, associate professor of cardiovascular medicine at Stanford. Despite the condition's enormous impact, few new treatments have been developed, and those that exist produce varied responses among patients. One major challenge to the development of new treatments has been the lack of genes that can be confidently associated with heart failure. Ashley is hopeful that the new finding will open doors to evaluating possible treatments.

The research is described in a paper published online Nov. 30 in the *Journal of the American College of Cardiology.* Ashley is the senior author. The lead author is Marco Perez, MD, assistant professor of cardiovascular medicine, who said the study was motivated by the observation that individual patients with heart failure often respond differently to the same types of medical interventions.

"We have noticed some patients with heart failure who get medical therapy respond really nicely," Perez said. "Their heart function improves dramatically with medications. Whereas other patients, despite medical therapy, continue to worsen and require transplant."

Perez wondered if there were genetic reasons for the discrepancies in treatment outcomes observed in the study. He suspected genetic variation in the study's patient group might point toward a link.

From men to mice

The team genotyped heart-failure patients at the extremes of responses — those who had the best and worst responses to therapy. They combined these results with gene expression data from human cardiac tissue available from a large, publicly accessible data set. By combining a variety of approaches including network modeling, which looks at the relationship between genes, the team searched for genetic variants associated with heart health.

Intrigued that their analyses spotlighted a gene near the region coding for the orexin receptor protein, which is known to be involved in the control of sleep, appetite and blood pressure, the team investigated further. Through a series of experiments, the researchers concluded that the gene likely regulates how much of the receptor is made in a cell. They then looked for evidence that the orexin receptor could be involved in heart function and found that its expression was increased in diseased human heart tissue. The researchers wondered whether this could mean that the receptor and its binding partner, orexin, have a protective function in the heart.

"We found this new receptor that looked very promising," said Ashley. "But what I'm most proud of is that the team didn't stop there; they went on to validate it in another data set, explore its mechanism in cellular models and then test the effect in several different mouse models."

Using a mouse model that mimics heart failure through artificially elevated levels of adrenaline, the researchers examined the role of the receptor and orexin. They found that if they gave orexin to the mice with failing hearts, those mice showed better systolic heart function — relating to the contraction phase of a heartbeat — than did mice that did not receive orexin.

Ultrasounds of the hearts in a different group of mice, which were missing the orexin receptor, showed that these mice had greater diastolic heart dysfunction — relating to the relaxation phase of a heartbeat — another hint suggesting that the receptor is important for healthy hearts.

"The exciting thing is that this gene is in a completely different neurohormonal axis — a completely different pathway than what has been looked at previously," Perez said. "Nobody had ever studied heart function in relation to this gene."

Other Stanford-affiliated co-authors are lab manager Ching Shang, PhD; research assistant Aleksandra Pavlovic; clinical nurse specialist Heidi Salisbury; former graduate student Khin Chan, MD; postdoctoral scholars Jing Liu, MD, Clint Miller, PhD, Frederick Dewey, MD, PhD, and Stephen Pan, MD; former postdoctoral scholar Porama Thanaporn, MD; professor of cardiovascular medicine Thomas Quertermous, MD; and associate professor of pediatrics Matthew Wheeler, MD, PhD.

MARK TUSCHMAN

Euan Ashley and his colleagues discovered an association between heart failure and a pathway linked to narcolepsy.

This research was supported by the National Institutes of Health, the Stanford Cardiovascular Institute, the Robert Wood Johnson Foundation, the Harold Amos Medical Faculty Development Award and the Breetwor Foundation.

Stanford's Department of Medicine also supported the work. ISM

Lindzi Wessel is a former science-writing intern at the School of Medicine Office of Communication and Public Affairs.

Study: Ancient viral molecules essential for human development

By Krista Conger

Genetic material from ancient viral infections is critical to human development, according to researchers at the School of Medicine.

They've identified several noncoding RNA molecules of viral origins that are necessary for a fertilized human egg to acquire the ability in early development to become all the cells and tissues of the body. Blocking the production of this RNA molecule stops development in its tracks, they found.

Vittorio Sebastiano

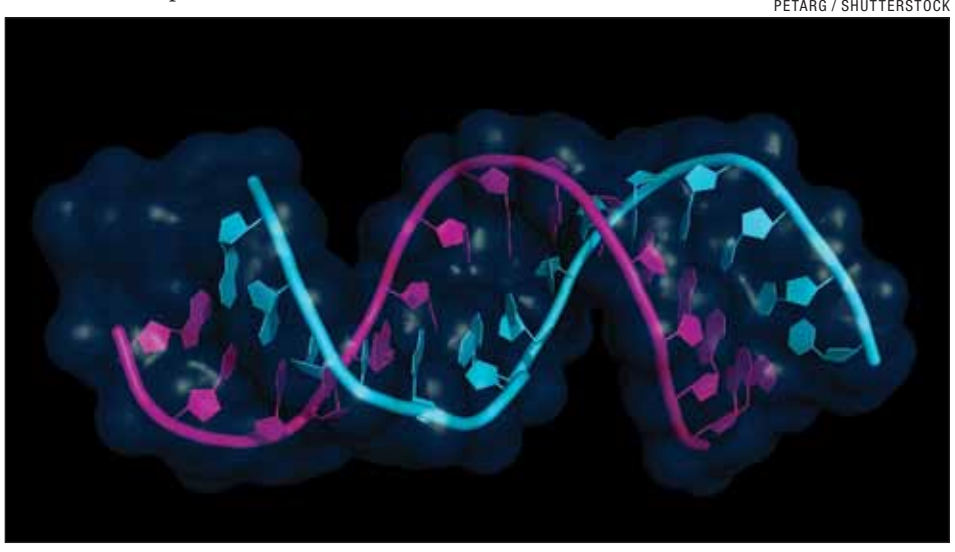
The discovery comes on the heels of a Stanford study earlier this year showing that early human embryos are packed full of what appear to be viral particles arising from similar left-behind genetic material.

"We're starting to accumulate evidence that these viral sequences, which originally may have threatened the survival of our species, were co-opted by our genomes for their own benefit," said Vittorio Sebastiano, PhD, an assistant professor of obstetrics and gynecology. "In this manner, they may even have contributed species-specific characteristics and fundamental cell processes, even in humans."

Sebastiano is a co-lead and co-senior author of the study, which was published online Nov. 23 in *Nature Genetics.* Postdoctoral scholar Jens Durruthy-Durruthy, PhD, is the other lead author. The other senior author of the paper is Renee Reijo Pera, PhD, a former professor of obstetrics and gynecology at Stanford who is now on the faculty of Montana State University.

Sebastiano and his colleagues were interested in learning how cells become pluripotent, or able to become any tissue in the body. A human egg becomes pluripotent after fertilization, for example. And scientists have learned how to induce other, fully developed human cells to become pluripotent by exposing them to proteins known to be present in the very early human embryo. But the nitty-gritty molecular details of this transformative process are not well understood in either case.

PETARG / SHUTTERSTOCK



Researchers have identified several noncoding RNA molecules of viral origins that are necessary for an embryo to acquire the ability in early development to become all the cells and tissues of the body.

An ancient infection

Using recently developed RNA-sequencing techniques, the researchers identified more than 2,000 previously unknown RNA sequences, and found that 146 are specifically expressed in embryonic stem cells. They homed in on the 23 most highly expressed sequences, which they termed HPAT1-23, for further study. Thirteen of these, they found, were made up almost entirely of genetic material left behind after an eons-ago infection by a virus called HERV-H.

HERV-H is what's known as a retrovirus. These viruses spread by inserting their genetic material into the genome of an infected cell. In this way, the virus can use the cell's protein-making machinery to generate viral proteins for assembly into a new viral particle. That particle then goes on to infect other cells. If the infected cell is a sperm or an egg, the retroviral sequence can also be passed to future generations.

HIV is one common retrovirus that currently causes disease in humans. But our genomes are also littered with sequences left behind from long-ago retroviral infections. Unlike HIV, which can go on to infect new cells, these retroviral sequences are thought to be relatively inert; millions of years of evolution and accumulated mutations mean that few maintain the capacity to give instructions for functional proteins.

After identifying HPAT1-23 in embryonic stem cells, Sebastiano and his colleagues studied their expression in human blastocysts — the hollow clump of cells that arises from the egg in the first days after fertilization. They found that HPAT2, HPAT3 and HPAT5 were expressed only in the inner cell mass of the blastocyst, which becomes the developing fetus. Blocking their expression in one cell of a two-celled embryo stopped the affected cell from contributing to the embryo's inner cell mass. Further studies showed that the expression of the three genes is also required for efficient reprogramming of adult cells into induced pluripotent stem cells.

Sequences found only in primates

"This is the first time that these virally derived RNA molecules have been shown to be directly involved with and necessary for vital steps of human development," Sebastiano said. "What's really interesting is that these sequences are found only in primates, raising the possibility that their function may have contributed to unique characteristics that distinguish humans from other animals."

Other Stanford authors are postdoctoral scholars Mark Wossidlo, PhD, Jonathan Davila, PhD, and Moritz Mall, PhD; research associate Diana Cepeda, PhD; former postdoctoral scholar Jun Cui, PhD; graduate student Edward Grow; Wing Wong, PhD, professor of statistics and health research; and Joanna Wysocka, PhD, professor of chemical and systems biology and of developmental biology.

The study was supported by the National Institutes of Health and the California Institute for Regenerative Medicine.

Stanford's Department of Obstetrics and Gynecology also supported the work. ISM

Neuroscience

continued from page 1

ner of Quarry Road and Welch Road, with an adjacent parking garage, and exam rooms, procedure rooms, faculty offices, a clinical trials office, a National Institutes of Health-funded research center on Alzheimer's disease, neurorehabilitation services, patient education and exercise classrooms, diagnostic imaging, radiological treatment services, a balance lab, a kinematic lab and an outdoor mobility garden, which features different kinds of surfaces for neuroscience patients to practice walking on.

The center also has two unusual testing services. The first is a PET/MRI scanner, a hybrid machine that produces images that are more accurate and detailed than in either technology alone — and with half the radiation exposure of a PET/CT scan. The center is one of the first health-care providers in North America to make this imaging available to patients who are not part of a research study. The second is the only comprehensive autonomic disorder testing laboratory on the West Coast. Disorders of the autonomic nervous system can be difficult to diagnose and treat without this type of lab and the appropriate specialists to interpret the results.

"The Stanford Neuroscience Health Center will provide the absolute leading edge of care in a highly coordinated fashion," said Amir Dan Rubin, president and CEO of Stanford Health Care. "This first-of-its-kind center brings together multidisciplinary teams of Stanford clinicians, leveraging breakthrough approaches, all in a highly patient-centered facility."

For multiple appointments, one check-in

Putting all these services in one place was one of the foremost requests of the Patient and Family Advisory Council: a group of 12 patients, who have been treated for neurological disorders, and their family members that was created to share perspectives with the center's designers. They did not want to be traipsing from building to building. The center has another time-reducer: Patients with multiple appointments in the center on the same day need only check in once.

> "To have this building that's been made specifically for us is astounding."

The advisory board also wanted other changes that might seem subtle, but make a difference to people whose neurological disorders affect their mobility. "The exam rooms are larger, the doors and hallways wider, the chairs sturdier and the floors organized logically to reduce the need for our patients to move from place to place," said the center's co-leader Frank Longo, MD, PhD, the George and Lucy Becker Professor in Medicine and professor and chair of neurology and neurological sciences. "We want our patients to come to our center and immediately recognize that it was designed to respond to their unique challenges in ways they have never seen in a care facility."

The check-in desk is low enough to be the perfect height for someone in a wheelchair. The center has a pharmacy certified to produce the customized medications given to patients by IV — just yards away from the infusion stations where patients sit for hours to receive those medications. The seats in that area were chosen because they can swivel 360 degrees, and the partitions are translucent and movable so people can talk to each other, or not.

Because some patients are sensitive to changes in floor texture, color and patterns, the center uses a muted palette; patterns have been kept to a minimum. The rare changes in floor covering are accomplished without the standard metal transition strips that are trip-and-fall hazards for people using crutches and an unpleasant bump for people using wheelchairs.

The center's administrators also conducted monthly simulations of what a patient might experience in the building, depending on which neurological disorder affected that person. "We wanted to fix any loopholes before the center opened," said center co-leader Gary Steinberg, MD, PhD, the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences and professor and chair of neurosurgery. "We wanted to do more than just institute innovations; we wanted to make sure they would work from the very first day we welcome patients to the new center."

Longo and Steinberg are looking forward, too, to the synergy of bringing together neurologists, neurosurgeons, interventional neuroradiologists and rehabilitation specialists. "One of the advantages of Stanford has always been the presence of people doing groundbreaking work in many fields. New ideas are born because we run into each other by accident. In this center, it won't be an accident," Steinberg said.

"I am sure that entirely new approaches to patient care will evolve because we have all of these disciplines together under one roof. We couldn't have done that in a conventional health setting," said Longo. "Many of our doctors are also involved in clinical research, and we wanted them to have a direct connection to patients. These clinicians are motivated every day by their patients to come up with better treatment options. Working in closer proximity means they can share their enthusiasm with each other and push the boundaries of what we can do for patients." ISM

PHOTOS BY NORBERT VON DER GROEBEN

Clockwise from above: Gary Steinberg and Frank Longo stand outside the Neuroscience Health Center, of which they are the co-leaders. Alison Kerr, a vice president for operations at Stanford Health Care, stands beside a check-in station in the center. Jinny Fruin (left), a member of the center's Patient and Family Advisory Council, and Luz Navarro, a radiology technician, take a stroll through the mobility garden, where neuroscience patients can practice walking on different kinds of surfaces.

Androgen

continued from page 1

prior institutional research agreement, 3.7 million patients from Mount Sinai Hospital, in New York City. Among this cohort, they identified about 9,000 prostate cancer patients at each institution, 16,888 of whom had non-metastatic prostate cancer. A total of 2,397 had been treated with androgen deprivation therapy.

Patients in the study who had been treated with ADT had about a 1.88 times increased rate of being diagnosed with Alzheimer's disease in a median follow-up period of 2.7 years compared with prostate cancer patients who did not receive ADT, the study found. The subset of men treated with ADT for longer than 12 months had a 2.12 higher risk — more than double that of prostate cancer patients not treated with ADT.

> "We're making secondary use of existing clinical data collected as part of routine medical care."

Using existing clinical data

Shah said the idea for the study started with Nead, who noticed some references in the medical literature to men who had ADT treatment for prostate cancer subsequently experiencing cognitive declines. "There was some chatter in the literature," said Shah. But no one had formally tried to find out if ADT therapy leads to cognitive defects.

"This is the kind of question that typically you would need a large clinical trial to answer," said Shah. But a formal clinical trial would be enormously expensive. "So instead, we're making secondary use of existing clinical data collected as part of routine medical care" — clinical data that's practically free.

Although ADT may increase the risk of defects in cognition and hand-eye coordination for reasons other than Alzheimer's disease, the team decided to focus specifically on Alzheimer's because the condition is easier to identify in medical records, said Shah. "Broader dementias and vascular dementia are kind of hard to quantify and define, so we had to narrow the scope of the analysis to make it feasible with the methods that we have available," he said.

After making statistical adjustments to control for biases, the team performed two kinds of tests to assess the reliability of the findings. In "falsification tests," they looked for false associations in the data. Specifically, they looked for five associations with medical conditions such as tuberculosis and allergies unlikely to be connected to testosterone levels. Those tests all came back negative.

They also looked for associations likely to be positive, such as age and cardiovascular disease — both conditions known to be associated with a risk of Alzheimer's disease. Those positive associations were confirmed in the data.

Patients who are receiving ADT and are concerned about the potential risks should discuss them with their physicians. "The association found in this study should be evaluated in the context of the overall treatment choices available to any specific patient," Shah said. "This study demonstrates the value of using existing EMR data to quantify the trade-offs that various treatments offer."

Stanford well-situated for work

Although other institutions are beginning to use patient records to ask and answer research questions, Stanford is unusually well-situated to do this work, said Shah. Patient records at Stanford are managed by the Stanford Center for Clinical Informatics. "If I was to go to another institution and ask for this same data, I'd probably be waiting a year, a year and a half; there would be so much hassle involved in being able to access the clinical documents that have detailed patient health information in them, whereas here we have the necessary infrastructure in place so that once you get Institutional Review Board approval, getting to the data doesn't take you a year and a half or two years," he said. Depending on the complexity of the data, it could take as little as two weeks at Stanford. Worst case, it could take six months, he said. "But it's not in geological time-scale."

The work was bolstered by electronic medical records shared by Mount Sinai Hospital, which doubled the number of relevant patient records — highlighting the importance of such cross-institutional collaborations. Harnessing the data in electronic medical records is part of Stanford Medicine's efforts in precision health — health care whose goal is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford-affiliated co-authors of the paper are medical student Gregory Gaskin; life science research assistant Cariad Chester; and associate professor of surgery and of medicine Nicholas Leeper, MD. The researchers collaborated with Joel Dudley, PhD, assistant professor of genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai.

This research was supported by the National Institutes of Health. Stanford's departments of Medicine, of Computer Science and of Radiation Oncology also supported the work

Shah is an inventor on patents owned by Stanford University that enable the use of clinical text for data-mining. ISM

Infertile men have a higher risk of heart disease and diabetes, study finds

By Lindzi Wessel

Men diagnosed with infertility have a higher risk of developing other general health ailments, including diabetes, ischemic heart disease, alcohol abuse and drug abuse, compared with fertile men, according to a study by researchers at the School of Medicine.

The study, published online Dec. 7 in *Fertility and Sterility,* is one of several conducted by investigators at the medical school that suggest male infertility is associated with higher rates of mortality and health problems unrelated to reproductive health.

The study's lead author, Michael Eisenberg, MD, assistant professor of urology and director of male reproductive medicine and surgery at Stanford, hopes the findings will encourage more men diagnosed with infertility to seek follow-up care.

"For members of this group of reproductive-age men, they usually don't go to the doctor unless there is a big problem," Eisenberg said.

"A lot of time fertility is one of the first things that brings them to the doctor, so in some ways that might be an opportunity to engage the health-care system and see what's going on with their general health."

Laurence Baker, PhD, professor of health research and policy, is the study's senior author.

Michael Eisenberg

Leveraging large databases

The researchers examined records filed between 2001 and 2009 of more than 115,000 reproductive-aged men from an anonymized insurance claims database. They analyzed the men's medical visits before and after fertility testing to determine what health complications they developed in the years after fertility evaluations. The researchers compared general health conditions of men with infertility diagnoses to those of men without the diagnoses and to those of vasectomized men.

Of the three groups, infertile men had higher rates of most diseases the researchers were screening for in the study, including heart disease and diabetes, even when results were adjusted for obesity, smoking and health-care utilization. In addition, men with the most severe form of male infertility had the highest risk of renal disease and alcohol abuse.

"It was surprising," Eisenberg said. "These were really young men. The average age was in the 30s."

Eisenberg and his colleagues are eager to pursue investigations to help determine why infertile men have a higher risk of certain diseases. "If we figure out why this is going on, we can target interventions to lower risks of these diseases," he said.

Mechanisms remain elusive

Researchers do not yet know why infertility is linked to higher rates of illness and mortality, but they have some theories.

Eisenberg noted that infertile men have lower levels of circulating testosterone than fertile men, a characteristic that has been linked to higher rates of mortality and cardiovascular disease.

Another possibility is that exposure to harmful environmental influences during fetal development could lead to both reproductive and general health challenges later in life. "Exposures that occur in utero can have lasting effects on the rest of your life," he said. "So maybe some of these same exposures that set men up later in life for things like heart disease could also set them up for things like lower sperm count."

Regardless of the reason, Eisenberg's research suggests that whatever is causing reproductive problems is likely to be influencing physiological systems, and he encourages men — particularly men experiencing reproductive difficulties — to get checked out.

"I think it's important to know that sperm counts and fertility may tell a little more than just about reproductive potential," he said. "There may be some other aspects that men could be alerted to about overall health."

Other Stanford co-authors of the study are statistician Shufeng Li and and Mark Cullen, MD, professor of medicine. Stanford's departments of Urology, of Dermatology and of Health Research and Policy supported the work.

Lindzi Wessel is a former science-writing intern at the School of Medicine Office of Communication and Public Affairs.

Optimal C-section rate may be as high as 19 percent

The most commonly performed operation in the world is cesarean section, and rates of cesarean childbirth delivery vary widely from country to country, from as little as 2 percent to more than 50 percent of live births. The World Health Organization recommends countries not exceed 10 to 15 percent (10 to 15 C-section deliveries per 100 live births) for optimal maternal and neonatal outcomes.

However, new research examining the relationship between C-section rates and maternal and neonatal mortality in 194 countries concludes that as the country-level C-section rate increases up to 19 percent, maternal and neonatal mortality rates decline. C-section delivery rates above 19 percent showed no further improvement in maternal and neonatal mortality rates.

The results were published Dec. 1 in the *Journal of the American Medical Association*.

Researchers from Ariadne Labs, a joint center of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health, and the Stanford University School of Medicine gathered and correlated national C-section, maternal and neonatal mortality rates in a single year (2012) for all 194 WHO member countries.

"On a nationwide level, our findings suggests there are many countries where not enough C-sections are being performed, meaning there is inadequate access to safe and timely emergency obstetrical care, and conversely, there are many countries where more C-sections are likely being performed than yield health benefits," said Alex Haynes, MD, MPH, the principal investigator of the study and associate director of Ariadne Labs' Safe Surgery Program.

Argument for improving surgical capacity

Thomas Weiser, MD, a co-author of the study and assistant professor of surgery at Stanford, said the research presents a compelling argument for improving surgical capacity in countries where access to care is limited. In doing so, countries will develop stronger, more resilient health care systems as a whole, he said.

"All the things you need to do to build up surgical capacity, like personnel training, improving supply chains, providing clean water and sterile environments, all contribute to general strengthening of health care systems," Weiser said.

The study emerges from ongoing research at Ariadne Labs and Stanford looking at access to surgical care as a key indicator of comprehensive health-care systems.

Other Stanford co-authors are Micaela Esquivel, MD, Tarsicio Uribe-Leitz, MD, and Tej Azad of Stanford.

No external funding was obtained for this study. ISM

Thalamus

continued from page 1

close to the electrode tip, including those in nearby but irrelevant tracts. It can't be used to pinpoint the circuit, or circuits, in which electrical stimulation is exerting its beneficial effect, much less to elucidate exactly how."

Interplay of brain structures

In the new study, Lee's group tracked the interplay among distinct structures throughout the entire brain — among them the thalamus, the somatosensory cortex and the zona incerta — and showed how this interplay regulates arousal states. To do this, they combined several approaches, including optogenetics, whole-brain functional magnetic resonance imaging, electroencephalogram and single-unit electrophysiology. This combination allowed Lee and her associates to excite or inhibit specific nerve cells at will in a cluster of nerve cells in the central thalamus of rats, while simultaneously observing resulting activity throughout the cerebral cortex.

Optogenetics entails installing light-sensitive proteins on the surface of selected nerve cells so that these cells, and only these cells, can be either excited or inhibited by specific frequencies of laser light delivered via a surgically implanted optical fiber. Whole-brain fMRI, with a resolution of less than one-fiftieth of an inch in each dimension, simultaneously monitors nerve activity levels in multiple brain regions. Single-unit electrophysiology — inserting microelectrodes into the brain and recording individual nerve cells' electrical activity — lets researchers zero in on circuits within zones of interest that have been flagged by the more global but less specific whole-brain fMRI technique.

The Stanford scientists experimented on otherwise normal laboratory rats that had been bioengineered so certain excitatory nerve cells in the central thalamus featured light-sensitive proteins on their surfaces. Laser light could be delivered through optical fibers to cause central-thalamic nerve cells containing those proteins to fire. The researchers stimulated the rats' brains with laser pulses at three different frequencies —10, 40 and 100 hertz. In each case, the stimulation proceeded in the form of 20-second bursts, once a minute, for six minutes, roughly mimicking the standard DBS cycle.

At all three frequencies, activity in the central thalamus increased. But the effects on brain areas receiving inputs from it were frequency-dependent: As shown by whole-brain fMRI, much more brain tissue in the frontal cortex was activated at 40 and 100 hertz than at 10 hertz. Stimulating the central thalamus at 10 hertz actually suppressed activity in the somatosensory cortex, a brain region that receives inputs from the central thalamus and is essential to maintaining alertness. The researchers validated this by monitoring individual somatosensory-cortex nerve cells using single-unit electrophysiology.

The suppression of somatosensory-cortex nerve cells at 10 hertz implied that inhibitory nerve cells from somewhere else must be intervening, and that their behavior was frequency-dependent.

The investigators next focused on the zona incerta, a structure below the thalamus consisting mostly of inhibitory nerve cells and known to send signals to the somatosensory cortex. This time, the researchers stimulated the central thalamus at 10 hertz and at 40 hertz while watching the effects in the zona incerta via single-unit electrophysiology and monitoring the forebrain with electroencephalography. They found that 10 hertz stimulation elicited electroencephalographic and electrophysiological waveforms characteristic of sleep or unconsciousness far more pronouncedly than 40 hertz stimulation did.

Effect of light frequency

Reasoning that the central thalamus was communicating with the zona incerta, Lee's group further bioengineered the test animals so that blue light would still fire up their excitatory central-thalamic nerve cells, but yellow light would shut down the inhibitory nerve cells in their zona incerta. Continuously stimulating these rats' central thalamic area with blue light, the researchers by turns suppressed or permitted zona incerta activity by switching the yellow laser on or off.

As expected, yellow light suppressed nerve-cell activity in the zona incerta, releasing the somatosensory cortex from the suppression observed earlier in the 10-hertz optogenetic stimulation of the central thalamus. Flicking off the yellow light switched on zona incerta nerve-cell activity, with suppression of activity in the somatosensory cortex resuming. The zona incerta was acting as a frequency-dependent circuit-breaker.

In a behavioral experiment, the researchers optogenetically stimulated the central thalamus of sleeping rats. At 10 hertz, the sleeping animals froze, in a manner suggestive of the behavioral arrest seen in people suffering from an absence seizure, which causes a brief lapse of awareness often characterized by a blank stare. (The condition is more common in children than adults.) At 40 or 100 hertz, the animals instantly woke up and started busily exploring their environments. EEG evinced waveforms associated with loss of consciousness in the 10 hertz case and of arousal at the higher frequencies.

Other Stanford authors of the study are research assistant Peter Lin; postdoctoral scholar ManKin Choy, PhD; and Robert Fisher, MD, PhD, professor of neurology and neurological sciences. Researchers from Cold Spring Harbor Laboratory in New York also contributed to the study.

Funding was provided by the National Science Foundation, the Alfred P. Sloan Foundation, the National Institute of Neurological Disorders and Stroke and Stanford Bio-X.

Stanford's departments of Neurology and Neurological Sciences, of Neurosurgery and of Bioengineering also supported the work. The Department of Bioengineering is jointly operated by the School of Medicine and the School of Engineering. ISM

Killifish project explores the genetic foundation of longevity

By Lindzi Wessel

Researchers at the School of Medicine have mapped the genome of an unusually short-lived fish, paving the way for scientists to use the organism to study how genes influence longevity.

The researchers published the genome map of the African turquoise killifish (*Nothobranchius furzeri*) Dec. 3 in *Cell*, along with early insights into the genetic determinants of its life span. Using a statistical analysis that looks at mutation rates across different organisms, the scientists found evidence that some of the same rare genes that have persisted in the killifish gene pool over centuries have also persisted in the gene pools of some unusually long-lived animals.

The researchers wonder if this means there are certain genes that evolution has "tuned" to create varying life spans.

"The range of life spans seen in nature is truly astonishing, and really we have very little insight into how this has evolved or how this works," said Anne Brunet, PhD, professor of genetics at Stanford and senior author of the study. "By having the genome of this fish and comparing it to other species, we start seeing differences that could underlie life span differences both between species and also within a species."

The study's lead author is Dario Valenzano, PhD, a former postdoctoral scholar in Brunet's lab who now directs his own lab at the Max Planck Institute for Biology of Aging.

Brunet and members of her lab have worked for the past nine years to establish a colony of killifish at Stanford and to create online access to killifish gene maps for other researchers who want to study them. They hope that studying the killifish, some strains of which live only four to six months, will help them investigate why some species, like this fish, live less than a year, whereas others, like some whales, can live 200. They also hope the research will provide insights into longevity differences among humans.

Life in the fast lane

Evolved to both hatch and reproduce within the brief rainy seasons in Mozambique and Zimbabwe, the turquoise killifish has an extremely compressed life cycle. Brunet said she and her team believed that once the fish's genes were mapped out, they would provide an "exciting new opportunity to use an evolutionary lens to propose ideas about aging."

Using a range of genomic and genetic techniques, team members sequenced small segments of killifish DNA and then used specialized software to string these sequences together until they had assembled a full digital map of the turquoise killifish genome. They repeated this process in different strains of the fish to identify important genetic variations within the species.

GREGG SEGAL

Anne Brunet and her colleagues are using the African turquoise killifish, above, as a model to study longevity and have provided its genetic information as a resource for the research community.

"Once you have the genome, it really breaks open the possibility of using genetic manipulation experiments and more conceptual comparative genomics studies," Brunet said.

Brunet and her colleagues have already begun to examine genes that are unique to the short-lived killifish, as well as to cross-breed short-lived killifish with a longer-lived strain to look for genes tied to longevity.

When they mated long-lived fish with short-lived fish, they observed a cluster of genes shared between the long-lived grandparents and the long-lived grandchildren. They noted that several genes in this cluster are associated with longevity and aging in other species.

One of these genes is the killifish equivalent of a human gene whose mutation is associated with frontotemporal dementia, a disease that generally manifests in late adulthood. The researchers see this as another good sign that analyses of killifish genes can set the stage for important health discoveries about human biology.

"We don't know yet exactly how these findings are relevant to humans, but these are questions we are actively pursuing," Brunet said.

A community resource

Brunet said she and her colleagues were eager to establish the killifish as a model organism not only for their own future studies but for the research community. As they worked to assemble the killifish genome, they also built a user-friendly website — http://africanturquoisekillifishbrowser.org — that other researchers can access for free.

"They can go to our website, enter their favorite gene of interest, and then zoom in on the killifish equivalent," she said.

The paper was published alongside another killifish genome paper by a German team in the same issue of *Cell*. Brunet said she is excited that other researchers have begun working with killifish and hopes the resources published by both teams will usher in a new level of emphasis on the animal as a model for longevity research.

"Having the genome transforms a nice, interesting organism into a model organism," she said.

GREGG SEGAL

Other Stanford-affiliated authors are postdoctoral scholars Bérénice Benayoun, PhD, Param Priya Singh, PhD, Chi-Kuo Hu, PhD, and Itamar Harel, PhD; research assistant Ben Machado; former research assistant Elisa Zhang; former technician Sabrina Sharp; former research associate Muh-Ching Yee, PhD; and Carlos Bustamante, PhD, professor of biomedical data science and genetics.

The research was supported by the National Institutes of Health Pioneer Award and Pathway to Independence Award, the Glenn Laboratories for the Biology of Aging, the Max Planck Institute for Biology of Aging, a Dean's Fellowship at Stanford, the Life Sciences Research Foundation Fellowship, the Stanford Center for Computational Evolutionary and Human Genomics Fellowship, the Damon Runyon Fellowship, the Rothschild Fellowship, the Human Frontiers Science Program Fellowship, and the German Federal Ministry of Education and Research.

Stanford's Department of Genetics also supported the work. **ISM**

Lindzi Wessel is a former science-writing intern at the School of Medicine Office of Communication and Public Affairs

OF NOTE

reports on significant honors and awards for faculty, staff and students

KANWALJEET ANAND, MBBS, DPhil, was appointed chief of palliative care and critical care medicine at Lucile Packard Children's Hospital Stanford and Stanford Children's Health. He was also appointed professor of pediatrics and of anesthesiology, perioperative and pain medicine, effective Oct. 1. He will lead the pediatric intensive care unit, which will expand from 24 to 36 beds in 2017.

GLENN CHERTOW, MD, MPH, the Norman S. Coplon/Satellite Healthcare Professor in Medicine and professor and chief of nephrology, was awarded the Belding H. Scribner Award by the American Society of Nephrology. He received the award in November at the society's annual meeting in San Diego.

C. GARRISON FATHMAN, MD, professor of medicine, received a 2015 Mayo Clinic Distinguished Alumni Award in November. The award recognizes the achievements of Mayo alumni in clinical practice, research, education and leadership who exemplify the clinic's ideals and mission. Fathman specializes in molecular and cellular immunology.

AMATO GIACCIA, PhD, the Jack, Lulu and Sam Willson Professor and professor of radiation oncology, has been appointed chair of the Basic Mechanisms of Cancer Therapeutics Study Section at the National Institutes of Health Center for Scientific Review. His term lasts through June 2017. He is director of the medical school's cancer biology program and co-director of the radiation biology program in the Stanford Cancer Institute.

DANIEL JAROSZ, PhD, assistant professor of chemical and systems biology and of developmental biology, was awarded a 2015 Packard Fellowship for Science and Engineering, one of 18 fellowships given by the David and Lucile Packard Foundation to support early-career scientists and engineers. He will receive $875,000 over five years. He specializes in the molecular biology of protein conformational switches and their influence on evolution, disease and development.

SEAN MACKEY, MD, PhD, the Redlich Professor, professor of anesthesiology, perioperative and pain medicine and chief of pain medicine, received the National Institutes of Health Director's Award in recognition of his leadership in the development of the National Pain Strategy. He co-chairs the oversight panel for the strategy, which is a national effort to advance pain care, education and research.

LLOYD MINOR, MD, the Carl and Elizabeth Naumann Dean of the School of Medicine and professor of otolaryngology-head and neck surgery, received the Joseph Toynbee Memorial Award from the Royal Society of Medicine and the Royal College of Surgeons of England in recognition of his achievements in otology and academic leadership. At the November ceremony in London, he delivered a lecture titled "My innovation journey: From lab to leadership."

PHILIP PIZZO, MD, former dean of the School of Medicine, was named a 2015 "Influencer in Aging" by NextAvenue, a PBS media provider for older Americans. He has also been appointed to the advisory board of the Milken Institute's new Center for the Future of Aging. Pizzo founded and directs the Stanford Distinguished Careers Institute. He is the David and Susan Heckerman Professor and a professor of pediatrics and of microbiology and immunology.

STEPHEN QUAKE, PhD, the Lee Otterson Professor in the School of Engineering and a professor of bioengineering and of applied physics, received the Jacob Heskel Gabbay Award in Biotechnology and Medicine from the Jacob and Louise Gabbay Foundation for advancements in the basic science of microfluidics and its applications to biomedical research. He received $15,000 and presented a lecture at Brandeis University in October. **ISM**

Kanwaljeet Anand

Glenn Chertow

C. Garrison Fathman

Daniel Jaroz

Sean Mackey

Lloyd Minor

Philip Pizzo