Neuroscience center to open for patient care

By Sara Wykes

Chris Bjornson, diagnosed with multiple telerosses 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, brain aneurysms, spine deterioration, Parkinson's disease and memory disorders, and other neurological and neurosurgical conditions. It is designed to provide patients with a state-of-the-art environment where they can receive optimal care in a setting that is focused on wellness and integration of mind and body.

"Five years ago, our neuroscience and neurosurgery experts 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."

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 means at Stanford. 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 center 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 center that is focused on wellness and integrates the most technologically advanced equipment with groundbreaking discovery.

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 counteracting 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.

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 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 neurosciences 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 route 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 nonspecifically triggers firing in all kinds of nerve cells.”

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 risk of developing Alzheimer’s disease diagnosis among those treated with androgen deprivation therapy.

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
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 continuous signals to the cell to divide uncontrolled.

Khavari is the senior author of the study, which was published online Nov. 23 in Nature Genetics. The lead author is Zurab Sprachvili, 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 causes a cell to divide uncontrollably or enables it to sidestep normal checkpoints that 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 instructs the cell to undergo repeated rounds of cell division. KRAS mutations are 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. Sprachvili 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, which results, the researchers say, in genes at much higher rate than normal. As errors accumulate in the genome, tumors develop more and more, and their disease.

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 lacked deleted SNORD50A/B were less likely than normal to survive.

“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.”

The researchers found that SNORD50A/B RNAs function in cancer as a brake on a protein called farnesyltransferase. Farnesyltransferase modifies a protein to protect the organism. These cells divide rampantly in the absence of normal biological checkpoints, which results, the researchers say, in genes at much higher rate than normal. As errors accumulate in the genome, tumors develop more and more, and their disease.

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They had this really amazing thing they had never expected. It was particularly surprising because my lab has been studying proteins for 30 years, more than a decade, so it was quite a coincidence.”

Goading cancer cells to divide

Sprachvili set out to find out more about the interaction between KRAS and SNORD50A/B. He found that when deleted SNORD50A/B in human normal and lung cancer cells grown in the lab, the cells divided more quickly and displayed more aggressive, dangerous traits than when present.

Finally, they showed that when SNORD50A/B binds to KRAS, it inhibits farnesyltransferase, an enzyme that adds a chemical group to a protein acting on anactivating 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,” Khavari said. “When SNORD50A/B is 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 cell into undergoing 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 RNA in this process could open new doors to blocking KRAS function in cancer.

This work 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, PhD; research assistant Hong Li, PhD; and postdoctoral scholar Alexander Ungewickell, MD, PhD; and Stanford Law School Associate Research Professor Ross Flockhart, PhD; postdoctoral scholar Brian Zarnegar, PhD; and professor of structural biology Joseph Pugli, PhD.

Stanford’s Department of Dermatology also supported the work.
Spyros Andreopoulos, former news director, died at 86

By Rosanne Spector

Spyros Andreopoulos, the director of Stanford Medicine’s news and public affairs office for 30 years until his retirement in 2009, was a key figure in educating the public about health care and biomedical research, died Nov. 20 at a nursing home in Menlo Park, California.

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 reporting on public relations specialists as an unusually well-informed, honest and sometimes bold broker of medical news.

When Andreopoulos walked into a room, Spyros was one of the most competent, most helpful and most completely honest people in the public information world,” said Dr. Lyle Nelson, Stanford University’s former executive vice president. “Spyros believed very firmly that you can’t hide things, and you shouldn’t hide things, and if some-thing happens at the university that is regrettable or bad, ourselves, we diminished the possibility of it be-coming a big scandal.”

As director of Stanford’s medical news office, Andreopoulos also served as spokesperson 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 1999.

Prolific writer

Other noteworthy Andreopoulos writings include the book Aging of America & the Role of the Academic Health Center (1988) and the article “The Ethical Alliance Between Academia and Cor- porate America” (2001) concerning the distorting influences of the commercialization of academic sci- ence on university research. He co-authored a medi- cal novel, Heart Beat, (1978).

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By Jennie Dusheck

Thousands of years ago lived a woman in the Egyptian city of Asyut, on the west side of the Nile 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 construction in the river that forced Asyut officials to stop traders carrying cargo downstream to the cities of the north and extract tolls from them.

Asyut is so at the north end of the infamous Darb el-’Arba’īn, the Forty Days’ Road, coming through the desert from Dairur. 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, some one 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. Hata son 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 mummy staging 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, an instructor of radiology at Stanford, collaborate with other specialists on the imaging project.

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 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.

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 longdead 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 wrapping was hollow except for her bones. Mary 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 enough, 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.
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 Evan Ash- ley, 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 pa- tients. One major challenge to the development of new treatments has been the lack of genes that can be con- fidently associated with heart failure. Ashley is hopeful that the new finding will open doors to evaluating pos- sible treatments.

The research is described in a paper published on- line 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. "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 mod- els 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 re- searchers examined the role of the orexin receptor and found that they had given the orexin receptor and others that made the mice had greater diastolic heart dysfunction — relating to the relaxation 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 the 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 com- pletely different neurohormonal axis — a completely different pathway than what has been looked at previ- ously," Perez said. "Nobody had ever studied heart func- tion in relation to this gene."

Other Stanford-affiliated co-authors are lab manager Ching Shang, PhD; research assistant Alexandra Pav- lovic; clinical nurse specialist Heidi Salibian; and former postdoctoral scholar Khin Chan, MD; postdoctoral schol- ars Jing Liu, MD, and Clinton Miller, PhD; Frederick Dewey, MD, PhD, and Stephen Pan, MD; former postdoctoral scholar Porama Thanaporn, MD; professor of cardio- vascular medicine Thomas Quertermous, MD; and as- sociate professor of pediatrics Matthew Wheeler, MD, PhD.

This research was supported by the National Insti- tutes of Health, the Stanford Cardiovascular Institute, the Robert Wood Johnson Foundation, the Harold Amos Medical Faculty Development Award and the Beatroot award.

Stanford’s Department of Medicine also supported the work.

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 Coomer

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 de- velopment to become all the cells and tissues of the body.’

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

‘We’re starting to accumulate evi- dence 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 Sebastiani, PhD, an assistant professor of obstet- rics and gynecology at Stanford who is now on the faculty of Montana State University.

Sebastiani and his colleagues were interested in learning how cells become pluripotent, or able to become any tissue in the body. A human egg becomes plu- ripotent after fertilization, for example. And scientists have learned how to in- duce 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 nutria- grity molecular details of this transfor- mative process are not well understood in either case.

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 em- bryonic stem cells. They homed in on the 23 most highly expressed sequences, which they termed HPAT1-23, for fur- ther study. Thirteen of these, they found, were made up almost entirely of genetic material left behind after an eons-ago in- fection by a virus called HERV-H. HERV-H is what’s known as a retro- virus. 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 assemble 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 retro- viral sequence can also be passed to fu- ture generations.

HERV, which has been linked with some cancers, is spread through most human tissues. But our genomes are also littered with se- quences left behind from long-ago retro- virus infections. Using HERV, which can go on to infect new cells, these retroviral sequences are thought to be relatively inert; millions of years of evolutionary and accumulated mutations mean that few maintain the capacity to give instructions for functional proteins.

After identifying HPAT1-23 in em- bryonic stem cells, Sebastiani and his colleagues studied their expression in hu- man blastocysts — the hollow clump of cells that arise from the egg in the first days after fertilization. They found that HPAT1-23 was present in placental tissue from one in four of the pregnancies they studied, and they found that these mice had greater diastolic heart dysfunction — relating to the relaxation 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 com- pletely different neurohormonal axis — a completely different pathway than what has been looked at previ- ously," Perez said. "Nobody had ever studied heart func- tion in relation to this gene."

Other Stanford-affiliated co-authors are lab manager Ching Shang, PhD; research assistant Alexandra Pav- lovic; clinical nurse specialist Heidi Salibian; and former postdoctoral scholar Khin Chan, MD; postdoctoral schol- ars Jing Liu, MD, and Clinton Miller, PhD; Frederick Dewey, MD, PhD, and Stephen Pan, MD; former postdoctoral scholar Porama Thanaporn, MD; professor of cardio- vascular medicine Thomas Quertermous, MD; and as- sociate professor of pediatrics Matthew Wheeler, MD, PhD.

This research was supported by the National Insti- tutes of Health, the Stanford Cardiovascular Institute, the Robert Wood Johnson Foundation, the Harold Amos Medical Faculty Development Award and the Beatroot award.

Stanford’s Department of Medicine also supported the work.

Vittorio Sebastiani and his colleagues discovered an association between heart failure and a pathway linked to narcolepsy.

Krista Coomer
There was some chatter in the medical literature to men 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.

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 Stanford Neuroscience Health Center will provide the absolute leading edge of care in a highly co-ordinated fashion,” said Amir Aghdasi, the CEO of Stanford Health Care. “This first-of-its kind center brings together multidisciplinary teams of Stanford — existing strengths, approaches, all in a highly patient-centered facility.”

For multiple appointments, one check-in

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“Broader demen-}

Shah said the idea for the study started with Neud, who noticed some references in the medical literature to men who had ADT treatment for prostate cancer subsequently experiencing cognitive de-}cines. “There was some chatter in the literature,” said Shah. But no one had

“Broader demen-}tias 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 in the data 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 to see if trends in the data were consistent with the results reported 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 car-}diovascular 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 physi}cians. “The association found in this study should be evaluated in the context of the lack of large-scale evidence of Stanford Medicine’s efforts in preci}sion health — health care whose goal is to provide everyone with the healthy and precisely diagnose and treat disease in the ill.”

The Stanford-affiliated co-authors of the paper are medical student Greg.}ory Gaskin; life science research as}sistant Caridad Chester; and associate professor of surgery and of medicine Nicholas Loeper, MD. The researchers collaborated with Joel Dudley, PhD, as}sistant professor of bioengineering and of computer science; Crystal Ong; and of Radiation Oncology also supported the work.

Shah is an inventor on patents owned by Stanford University that enable the clinical text-mining engine to work.
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, was based on data from 1,020 men who had been patients at fertility clinics and who were consulting with male reproductive endocrinologist and surgery at Stanford.

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 ways like that might be an opportunity to engage the health-care system and to start getting on with their general health.”

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

Leveraging large databases

The researchers examined records filed between 2001 and 2009 of more than 115,000 reproductive-aged men from an anonymous insurance claims database at two fertility clinics. After data collection 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 fertile 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, the study found.

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 improved health and mortality, but they have some theories.

Eisenberg noted that infertile men have lower levels of fertility hormones 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 men get up later in life for things like heart disease could also set them up for things like lower sperm count.”

Regardless of 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 marks a line, but it’s just about reproductive potential,” he said. “There may be some other aspects that men could be alerted to about their overall health.”

Other Stanford co-authors of the study are statistician Shufeng Li and Mark Cullen, MD, of medicine; Leslie E. Overman, PhD, of Urology, and Damodar of Health Research and Policy supported the work.

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

Thalamus

Michael Eisenberg

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 thalamus using distinct electrodes throughout the entire brain — among them the thalamus, the somatosensory cortex and the zona incerta — and showed how this interplay regulates arousal. To do this, they combined several approaches, including optogenetics — using a brain functional magnetic resonance imaging, electroencephalograph and single-unit electrophysiology. This combination of optogenetics 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 activity throughout the cerebral cortex.

Optogenetics entails inserting lighting-sensitive genes onto the surface of selected nerve cells so that these cells, and only these cells, can be either excited or inhibited by specific frequencies of light delivered via a surgically implanted optical fiber. Whole-brain MRI, with a resolution of no finer than 1.5 millimeters, can track the thalamus in a rodent brain, while EEG monitored the surface activity of activity often characterized by a blink arrest. (The condition is more common in children than adults.) At 40 or 100 hertz, the animals instantly woke up and started busily exploring their environment.

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 blink arrest. (The condition is more common in children than adults.) At 40 or 100 hertz, the animals instantly woke up and started busily exploring their environment. EEG waveforms associated with loss of consciousness for the blink arrest were more pronounced than 40 hertz stimulation did.

Effect of light frequency

Reasoning that the central thalamus was communicating with the zona incerta, Lee’s group further increased the test animals so that blue light would first stir up their excitatory central-thalamic nerve cells, but yellow light would later suppress the impulses in the zona incerta. Continuously stimulating these rats’ central thalamic area with blue light and suppressing 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, suppressing 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-discriminating relay.

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Killfish 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 genome 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. “In the future, if 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 between species and also within a species.”

The study’s lead author is Darwin 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 genome maps for other researchers who want to study them. They hope that studying the killifish, some strains of which live only for 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 that the research will provide insights into longevity differences among humans.

Life in the fast lane

Evolved to both harch 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 ponder questions 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. “Once you have the genome, it really breaks open the possibility of using genomic 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 progeria, 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 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://african turquoisekillifishbrowser.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 research 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.

Other Stanford-affiliated authors are postdoctoral scholars Béatrice Benarouche, 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 PhD student Muh-Ching Yee, PhD; and Carlos Bustamante, PhD, professor of biomedical data science and genomics.

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 Utam 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.

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