Male infertility linked to higher risk of mortality

By Bruce Goldman

Men who are infertile because of defects in their semen appear to be at increased risk of dying sooner than men with normal semen, according to a study led by a researcher at the School of Medicine.

Men with two or more abnormalities in their semen were more than twice as likely to die over a roughly eight-year period as men who had normal semen, the study found.

Smoking and diabetes — either of which doubles mortality risk — both get a lot of attention, noted the study’s lead author, Michael Eisenberg, MD, PhD, assistant professor of urology and Stanford’s director of male reproductive medicine and surgery. “But here we’re seeing the same doubled risk with male infertility, which is relatively understudied.”

Infertility is a widespread medical complaint in developed countries, where about one in seven couples is affected at some point. But this is only the third study worldwide, and the first in the United States, to address the question of a connection between male infertility and mortality, said Eisenberg. Results from the two earlier studies, one in postwar Germany and another in China, have finally gained delivery until what if nuclear bombs could reproduce? Get your hands on one today, and in a week’s time you’ve got a few dozen.

Of course, nukes don’t double on their own. But contagious, one-celled pathogens do. Properly packaged as a bioweapon, they could kill as many people as a hydrogen bomb would, or more.

Milana Trounce, MD, a clinical associate professor of emergency medicine, wants to get people to worry about this possibility. For the fourth year in a row, she is presiding over a course called Biosecurity and Bioterrorism Response, which aims to get students thinking about how to prevent bioterror and, in the event of a biological attack, what to do about it. More than 100 Stanford undergraduate, graduate, postdoctoral and professional students, representing disciplines ranging from public policy to biological science to engineering and bioengineering, have enrolled.

The course, which Trounce considers more of a forum or workshop, brings students together with guest lecturers from Stanford and other universities, as well as with biotech-company executives, think-tank denizens and current and former public-health and other government officials.

“I’m hoping to continue to grow this forum to figure out real-world solutions,” said Trounce. Authorities on bioterrorism and biosecurity say that more thinking about how to handle this threat is desperately needed. Steven Block, PhD, professor of biological sciences, offers a course called Biosecurity and Bioterrorism Response, which aims to get students thinking about how to prevent bioterror and, in the event of a biological attack, what to do about it.

How contagious pathogens could lead to nuke-level casualties

By Bruce Goldman

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Student project thanks the often-unsung teachers of medical school: the patients

By Tracie White

Perhaps the most important teachers in a medical student’s career are patients. Without them, a student could never become a doctor.

In an effort to honor these often-unsung teachers, a group of fourth-year medical students started a project, The Thank-You Cards You Have Yet to Send, by hand-delivering thank-you cards to their classmates. The 35 or so cards they got back are filled with heartfelt sentiments from medical students to patients describing just how important they have been on the students’ journey to becoming physicians.

To a patient dying of cancer: Thank you for teaching me that when I no longer have anything to offer you from the science of my craft, that I can still offer you the companionship of my humanity.

The project grew out of a desire to show appreciation for patients who have touched us emotionally or intellectually. It was displayed in April at the Medicine and the Muse Symposium.

The main idea was that after four years of medical school, we’ve thanked family, friends and teachers. But a large part of our clinical training has come from patients,” said Jai Madhok, another project organizer.

By putting the cards on display, the students hope that the messages — which do not name either the writer or the recipient because of confidentiality concerns — still somehow reach patients.

“Realizing that when you come back the next day, your patient might not be there, that’s hard to grapple with,” Madhok said. He wrote a thank-you note to a stroke patient who he helped care for during the last days of the patient’s life:

I will always remember that you asked me for an ice-cold Slurpee from 7-Eleven in broken words when you finally gained

In a project titled The Thank-You Cards You Have Yet to Send, medical students recognize the importance of patients as teachers.

A way to stop insulin delivery when blood sugar gets low at night

By Erin Digitale

New research could soon make it easier for people with type-1 diabetes to get a safe night’s sleep, says a School of Medicine scientist who led the study.

In a large trial conducted in patients’ homes in the United States and Canada, scientists demonstrated that they could predict and prevent dangerously low overnight blood sugars in adolescents and adults with type-1 diabetes.

Very low blood-sugar levels can cause seizures or even, in rare cases, death. People with type-1 diabetes often sense warning signs of low blood sugar when they are awake, but not during sleep, explaining why 75 percent of diabetic seizures occur at night.

The new study, published online May 7 in Diabetes Care, coupled a glucose sensor worn under the skin to an insulin pump that was connected wirelessly to a computer at the bedside. The computer ran an algorithm that calculated when a low blood-sugar level might occur and then temporarily suspended insulin delivery until
**Inhibiting protein family helps mice survive radiation exposure**

By Krista Conger

Tinkering with a molecular pathway that governs how intestinal cells respond to stress can help mice survive a normally fatal dose of abdominal radiation, according to a new study by researchers at the School of Medicine.

Because the technique is still partially effective up to 24 hours after exposure, the study suggests a possible treatment for people unintentionally exposed to large amounts of radiation, such as first responders at the Chernobyl nuclear disaster in 1986.

“We were very surprised by the amount of protection the animals received,” said Amato Giaccia, PhD, professor of radiation oncology. “The important thing note is that we didn’t change the amount of damage the intestinal cells sustained as a result of the radiation; we simply changed the physiology of that tissue and how it responded to that damage.”

The researchers believe that a similar approach may also help protect people from radiation exposure from a bone marrow transplant, there’s no treatment for its long-term complications. Black babies, in particular, are extremely susceptible to infection. Although radiation kills cells by irreversibly damaging their DNA, some cells can survive at low levels of radiation typically experience debilitating nausea and vomiting when their intestines lose the ability to properly regulate fluid exchange. They are also extremely susceptible to infection. Although radiation exposure are seen most clearly in rapidly dividing cells, such as those found in the lining of the intestine or blood and immune cells in the bone marrow. People who have undergone exposure to high levels of radiation typically experience debilitating nausea and vomiting when their intestines lose the ability to properly regulate fluid exchange. They are also extremely susceptible to infection. Although radiation

**Racial disparities seen in rates of ER visits by newborns**

By Patricia Waldron

During the first month of life, African-American newborns are brought to the emergency department at roughly twice the average rate of all newborns, according to a study led by a researcher at the School of Medicine.

When newborns visit the emergency department, they can be exposed to infections carried by other patients, which can be deadly to their underdeveloped immune systems. “We don’t want anybody to get sick in the emergency room, but particularly for a baby in the first month of life, they’re just very vulnerable,” said Henry Lee, MD, assistant professor of pediatrics, a leader of the study.

The study did not delve into why black newborns visit the ER more often. The higher number of visits may stem from both medical and socioeconomic causes, Lee said. The researchers speculate that the parents of black newborns may not be getting the resources or help they need to transition care for their infants from the maternity ward to a primary-care clinic.

The researchers describe their findings in a paper published online May 2 in *Diabetes Care.*

In the study, Lee and his colleagues analyzed data from the National Hospital Ambulatory Medical Care Survey. This survey collects information from emergency department visits at hospitals nationwide. It’s maintained by the National Center for Health Statistics. The study team focused on the age of the babies, whether they were insured and the type of hospital they were brought to. The researchers also used the survey to distinguish visits by race.

The study found that each year, more than 320,000 newborns visit an emergency department during their first four weeks, representing 7.6 percent of all babies. But when the researchers took into account the race of the patients, they found that 14.4 percent of black babies visited an emergency department—a little more than twice the rate of white babies, which were 7.7 percent. For non-Hispanic white babies, the rate of emergency room visits was 6.7 percent.

The researchers were unable to account for a family’s income but found that black mothers were more likely to have given birth in safe-net hospitals, which serve larger numbers of low-income or uninsured patients, than white mothers. But this finding alone does not explain the discrepancy; Hispanic mothers also delivered in safety-net hospitals more often than white mothers.

“The reasons behind the observed differences in newborn visits are unclear,” said Antonio Riera, MD, an assistant professor of pediatric emergency medicine at the Yale School of Medicine.

Many newborns visit the emergency department for reasons that may not be obvious at birth. Black and Hispanic babies are more likely to be born into low-income families than white babies, according to the U.S. Census Bureau, and poorer families often have a hard time getting to check-ups and paying for medical care. Also, some mothers may not have the same level of support from friends and family to advise their newborns. Sometimes babies have to visit the emergency department— for instance, if they have an infection or an inherited disorder that is not obvious at birth. In Lee’s study, almost two-thirds of the newborns’ emergency department visits were for issues that likely required emergency care. But some visits are preventable, such as when a baby has a problem that was missed by providers at the hospital or when the parents take their baby to an emergency department instead of to a clinic for well-baby checkups.

A pediatrician should examine all babies within the first week of life to assess whether they are growing and developing normally. “Ideally, when a baby leaves the hospital, there is a first visit with the clinic pediatrician already scheduled,” said Lee. During this follow-up visit, the well-baby pediatrician would check for common problems, such as jaundice, and ensure that the baby is feeding properly.

“Pediatricians would also help to answer any questions that the parents may have, particularly for first-time parents,” Lee added. But if the hospital does not arrange a visit and parents do not have a pediatrician already picked out, then some babies could end up in the emergency room for routine care.

Additional research is needed to determine what percentage of emergency department trips are unnecessary, and how those visits can be cut down to reduce health-care costs, Lee said. Earlier studies have shown that up to 60 percent of infant visits to the emergency department could have been handled at a clinic. Lee speculates that hospitals could decrease the number of visits by easing the transition from the hospital to a clinic. If families receive a referral to a pediatrician early on, they may be less likely to use emergency medical services for nonurgent illnesses.

Increasing the quality of care at the birthing hospital for underserved families may be another way to cut down on emergency visits, said Lee. If hospitals properly screen infants for common problems, feeding issues and infection, then they may be able to reduce re-admissions.

Doctors can also counsel new parents about when they should make a trip to the emergency room, and when an issue can wait until morning.

A better understanding of why black newborns visit the emergency room more often than other groups could also point our ways to simultaneously reduce visits and to provide better care. “Improving the quality of care for this higher-risk group could also help to improve disparities and outcomes as well,” Lee said.

Researchers at the University of California-San Francisco collaborated with Lee on the study, which was funded by the Ennace Kennedy Shriver National Institute of Child Health and Human Development.

Patricia Waldron is a science-writing intern for the medical school’s Office of Communication & Public Affairs.
Employee recognition award winners announced

By Mandy Erickson

The Stanford School of Medicine recently announced this year’s winners of the Spirit Award and the Inspiring Change Leadership Award. The Spirit Award, given to staff members who show outstanding performance, dedication and positive attitude, went to Christopher Dolph, Willed Body Program coordinator and lab coordinator in the Division of Clinical Anatomy, and to Anne Crowe, assistant director of the Center for Biomedical Ethics.

Christopher Dolph
Every so often, when Stanford medical students are slicing open cadavers for anatomy class, a caped figure will swoop through the lab: It’s Captain Dissector! He’s here to make sure you’re having fun.

“You never know when he’s going to show up,” said Dolph, the anatomy lab coordinator, who created Captain Dissector one summer when a group of high school students were learning about anatomy. He decided the crowd, surrounded by dead bodies, needed to lighten up.

“You have to have a little humor in this business or it’ll chew you up,” he said. Dolph accepts cadavers that have been donated to the lab. Before they need to arrive within 24 hours of death, he’s on call 24/7, making sure the body is fit for dissecting and coordinating its arrival to the school. He then embalms the bodies so they’re ready for students.

Sometimes he speaks directly to family members: “It can get pretty gut-wrenching,” he said. “They start talking about how they met their loved ones, how many children they had. A lot of times I just have to listen for a while.”

Sakshi Srivastava, MD, associate professor of anatomy, said Dolph skillfully balances the need to inject fun into the dissecting room with respect for the deceased. “He’s doing that wonderfully well,” he said. “He truly is the spirit of the lab.”

Dolph, who has worked at the medical school for 21 years, began as a 12-year-old helping his father, John Dolph, in the cadaver lab. He took over the job after his father retired, about 10 years ago. When he earned the award, he said, “I took it as much as an honor to my father as to me. The first call I made was to Pops.”

Anne Crowe
When Crowe took on the position of assistant director of the Center for Biomedical Ethics six years ago, her boss, David Magnus, PhD, found that the time she spent on administrative tasks plummeted.

“Once Anne came on board, the amount of work I had to do as center director dropped by 90 percent. She manages everything so seamlessly,” said Magnus, the center’s director and the Thomas A. Raffin Professor in Medicine and Biomedical Ethics. “She is an absolute model of professionalism. She puts the center above everything else.”

After earning an MBA at the University of San Francisco, Crowe held a similar job with the engineering department at UC-Berkeley before she came to the Stanford center to oversee finances and administration. On the financial side, she creates budgets, handles grants and oversees the operational expenses. As for the administration, Crowe’s job covers everything in running a center of two faculty members, 13 researchers and four administrative staff. She oversees procurement, facilities and human resources, including hiring and supervising administrative staff and helping with personnel evaluations.

“It’s a dream job,” Crowe said. “It’s the perfect combination of a really interesting and diverse set of duties in a forward-thinking, scientific environment, working with brilliant people.”

“This award is an honor. It means that how I’ve been performing at this job is appreciated,” she added.

Crowe “loves the center,” added Magnus. “She’ll do anything for it. She’s unflappable.”

Aarti Porwal
Soon after moving from Chicago to become the manager of strategic initiatives in education at the medical school, Porwal was handed a massive task: overseeing the school’s accreditation renewal.

The two-year process required answering about 1,000 questions from the Liaison Committee on Medical Education, coordinating with 300 people at the school for an institutional self-study, and days of interviews with LCME members. When it was complete, Stanford received only one citation — a stellar result, down from three issued after the previous accreditation.

“Aarti went through the last LCME review and the current LCME standards and constructed a dashboard of what LCME was looking for,” said David O’Brien, director of institutional planning. “No one had done that before. She was very innovative in coming up with tools like that.”

On the job, Porwal was able to identify and correct issues before they became citations. “We were almost harder on ourselves than they were,” said Porwal, who had never taken on accreditation before. “We were very pleased with the outcome.”

Porwal also designed the LCME process with a focus on continuous quality improvement, which has allowed the school to identify additional opportunities for improvement beyond accreditation.

“Now that the school has been accredited for the next eight years, Porwal is back doing what she was hired to do: executing the dean’s plans to improve the medical school. ‘She does it phenomenally well,’ O’Brien said.

Porwal is receiving the Inspiring Change Leadership Award “is probably the most meaningful thing that has happened to me in my career. I was pleased to receive it, but it really was a huge team effort.”

Usha Chhiba
Chhiba, manager of the Division of Neonatal and Developmental Medicine, takes a systemic approach to problem solving.

“Usha isn’t one to look at a problem and figure out a way to get it off her desk and off her mind,” said William Benitz, MD, division chief and the Philip Sunshine, MD Endowed Professor in Neonatology. “She’s always asking questions: ‘What is the structure that’s causing these problems to bubble up?’ ‘How can we change this?’ She pays attention to the underlying process.”

For example, after Chhiba moved into the division manager position two years ago, she noticed that the quarterly reports for grant expenditures lacked cohesion. So she came up with a template that provides a broad view of the grant’s finances.

“It’s an easy tool to use for projections,” she said. “It’s worked out quite well.” The financial analyst now uses the tool for monthly portfolio reviews with principal investigators — and the medical school later required every department to hold similar monthly meetings.

The Inspiring Change Leadership Award “validates the work we’ve been trying to do to make some improvements,” Chhiba said. “It means a whole lot for the whole team.”

Benitz said Chhiba is always willing to share her administrative expertise with other divisions within pediatrics, and even outside the department. “She does it in a really nice, unobtrusive way that can be really helpful without appearing superior,” he said.

“She’s just been a delightful partner for me,” he added. “We work really well together.”

Honor roll: Employees mark big anniversaries at medical school

All university employees who are celebrating 30, 35, 40, 45 and 50 years at Stanford will be honored at a celebration May 22 that begins at 11 a.m. in Frost Amphitheater.

School of Medicine employees who have served for 30 years:
• Bonita Baker, social science research assistant, Department of Pediatrics
• Susan Gonzalez, administrative associate, Department of Orthopaedics
• Tim Knaak, life science research assistant, Center for Molecular and Genetic Medicine
• Eileen Mains, administrative associate, Department of Pathology
• Angela Mayorga, computing information systems analyst, Research Management Group
• Dick Miller, librarian, Lane Library
• Robert Schneeweis, science and engineering associate, Department of Neurobiology
• Cariel Taylor-Edwards, life science research assistant, Department of Medicine

Those who have served for 35 years:
• Mary Buttnet, librarian, Lane Medical Library
• Cheryl Joo, administrative services manager, Department of Neurology
• Debbie Leong-Childs, finance services manager, Research Management Group
• Lisa Ma, life science research assistant, Department of Pathology
• Rebecca Shreve, administrative services manager, Department of Psychiatry and Behavioral Sciences

Those who have served for 40 years:
• Miguel Alvarez, animal care supervisor, Department of Comparative Medicine
• Ronald Garcia, academic research and program officer, Center of Excellence in Diversity in Medical Education
• Norma Malimban, laboratory assistant, Department of Biochemistry

The Inspiring Change Leadership Award, for staff members who have implemented processes that improve the school, went to Aarti Porwal, manager of strategic initiatives for education in the Office of Institutional Planning, and to Usha Chhiba, manager of the Division of Neonatal and Developmental Medicine. Each award winner received $3,000.
Bioterror continued from page 1

and of applied physics at Stanford, is a member of a scientific advisory group that meets several times a year to report to the federal government on national security issues, including bioterrorism.

“The advent of modern molecular genetic

A natural anthrax strain mailed to public officials in a series of homegrown terrorist incidents in late 2001 — while deadly, was treatable, Block said. But the technology for making drug-resistant anthrax — or, for that matter, creating all manner of novel "designer diseases" — is becoming increasingly available worldwide, not to mention cheaper and more sophisticated.

"It blew my mind," Trounce commented. "As a citizen, I had had no idea these facilities even existed. To come as a U.S. citizen and see these facilities — where thousands of scientists had been working on the deadliest pathogens was unbelievable. Who knows what I didn't see?"

"Did that massive Soviet bioweapons inventory ever get entirely dismantled?" Trounce asked. "I don't think anybody really dismantled it if they do it's classified information. What we do know is that there are three Russian Ministry of Defense bioweapons laboratories that are not in the public domain."

Retired Rear Adm. Ken Bernard, MD, a guest speaker for the course, said, "You can say 'don't build a nuclear weapon' and you can say 'don't build a biological weapon," "But there's no need to create a brand-new organism from scratch. Lots of people have proteins or biologicals made, of course. They have the raw materials and know their way around labs."

"Those skills they've learned, he noted. "That's one of the scariest organisms — for example, smallpox."

"In laboratory experiments, scientists have mutated F5NII — a deadly influenza strain that so far has been transmitted to humans only by birds — to become transmissible by other humans. They have synthesized the Spanish flu virus, a naturally occurring strain that swept the globe in a 1918 pandemic, killing far more people than died in all the battles of World War I. What if any of those were to get out of the lab?"

"Unfortunately, it's a real possibility, because with advances in technology it's now much easier to create these weapons than ever before," Trounce said. "A few people with modern resources can create a bioweapon. This is something we don't typically think about."

"Something old, something new"

Long before the advent of high-tech laboratories, bioweapons had earned a perch in the annals of infamy. The ancient Romans, like others before them, threw into wells to poison their adversaries’ drinking water. In 347, the Tartars catapulted the bodies of bubonic-plague victims over the defensive walls of the Crimean Black Sea port city now called Feodosia, then a defensive walls of the Crimean Black Sea of bubonic-plague victims over the de-

A rendition of anthrax bacteria (left). A natural strain of the pathogen mailed to public officials in a series of homegrown terrorist incidents, in late 2001, was deadly but treatable, said Steven Block (above). But the technology for making drug-resistant anthrax — or, for that matter, creating all manner of novel "designer diseases" — is becoming increasingly available worldwide, not to mention cheaper and more sophisticated, he said.

"I was under a biotechnology revolution," she said. "Even in the last 10 years, science has advanced so much that you can engineer some of the scariest organisms — for example, smallpox."

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you can trace material by its composition ‘signa- 
re,' said Tronc. "Biological agents are ubiqui-
tous. You could even obtain them within the target area. It’s important to figure out who the bad guy is. That’s ideal for terrorism." 

Progress since 9/11? 

There was a big expansion of public-health funding at the federal level in the first five years or so to deal with some of those very early post 9/11. ‘We’ve come a long way to solving the mass-
smallpox scenario problem,’ Bernard said. Smallpox—a viral pestilence characterized by high rates of mortality and serious complications that spread from the front-
head to the feet within two or three days, and the breakdown of multiple bodily organs—
killed an estimated 300 million to 500 million people in the 20th century. Smallpox would be very hard for a terrorist to get his hands on, but if he could get them in the United States, and one in Russia, Bernard said. ‘In the old days everybody in the United States used to get vac-
nated for smallpox. We stopped in the 1970s, ex-
cept for the military. Everybody under 34 years old—more than half of our population—has never been immunized.’

Working in the White House under President George W. Bush, Bernard spearheaded Project Bioshield, a $5.6 billion initiative to hand out grants to the public health community. Among the products being developed under the Bioshield egg are two new antivirals for small-
pox; antibodies to neutralize smallpox that’s safe for immu-
nocompromised people, pregnant women, and people with eczema whose permeable skin makes the traditional live-virus-based vaccine risky.

Like aircraft carriers, anti-bioterror medical plat-
forms in major cities. The system has its warning system for dangerous microorganisms. Germ-monitoring sensors are attached to ex-
isting environmental air-quality-sampling platforms in major cities. The system has its drawbacks, though. A few false alarms have been triggered, and it takes a full 24 hours to get re-
sults, which could be too late.

Early, accurate diagnosis is crucial, said Rel-
man. ‘In a lot of cases, people benefit from an-
timicrobial drugs only if they start taking them within 48 hours—and they’ve got to be taking the right drug. It is also the hardest time to get an accurate diagnosis, because the earliest phases of many of these diseases are often nonspecific.’

But if anything, Relman said, ‘the situation has gotten worse in the past decade as budgets for the Centers for Disease Control and Pre-
vention and for state and local health facilities have been actually cut. We know we need much greater surge capacity, for example hospitals to take care of respiratory illness. But we haven’t in-
vested in public health, and it is dying by attrition.’

It’s politically tough to justify expenditures for things that haven’t happened. Relman added.

‘There are such strong links between bio-
security and terrorism. That’s one of the hardest things to convince policymakers to think about.’

The memory in question was related to the ability to perform an abdominal radiation exposure, 45 percent of the treated animals, but no un-
treated animals lived beyond 10 days.

Although the study suggests a possible way to mini-
gate the effects of therapeutic radiation exposure, much work remains to be done, the researchers caution. For one thing, mice are more resistant to the effects of radiation than humans, and the radiation doses used in the study far exceed what would be used to treat a cancer patient. But the next steps are clear.

‘There are a number of drug molecules that act in a manner similar to DMOG that are already in clinical tri-
als,’ said Giaccia. ‘Our next step will be to test some of these molecules to see if they also offer radioprotection.’

Other Stanford authors of the study include post-
doctoral scholars Yu Rebecca Miao, PhD, Colleen Wu, PhD, Erin Rankin, PhD, Todd Atwood, PhD, graduate student Kaitlin Chang, and director of radiation physics Lei Xing, PhD.

A patent application, titled ‘Use of Prolyl Hydroxylase Inhibitors as a Radioprotective Drug for the Lower Gastrointestinal Tract’ (International Application No. PCT/US2012/052232) was filed based on the results of this study. The research was supported by the National Institu-
tes of Health, the Radiological Society of North Amer-
ica Resident Research Grants, the Canadian Institutes of Health and Research, the Silicon Valley Foundation and the Sydney Frank Foundation.

Network launched to connect musicians, music lovers

By Jacqueline Genovese

A shared memory of attending a 1976 cello performance by Yo-Yo Ma, then a student at Brown, nor Goodman, a stu-
dent at Harvard, helped to inspire the creation of a network to bring together musicians and music lovers in the Stan-
ford Medicine community.

The memory in question was related to Steve Goodman, MD, PhD, assoc-
iate dean for research and translational science, during a meeting for the Stan-
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A patent application, titled ‘Use of Prolyl Hydroxylase Inhibitors as a Radioprotective Drug for the Lower Gastrointestinal Tract’ (International Application No. PCT/US2012/052232) was filed based on the results of this study. The research was supported by the National Institutes of Health, the Radiological Society of North America Resident Research Grants, the Canadian Institutes of Health and Research, the Silicon Valley Foundation and the Sydney Frank Foundation.

“Network launched to connect musicians, music lovers”

By Jacqueline Genovese

A shared memory of attending a 1976 cello performance by Yo-Yo Ma, then a student at Harvard, helped to inspire the creation of a network to bring together musicians and music lovers in the Stanford Medicine community.

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Lloyd Minor, dean of the medical school, co-founded the Stanford Medicine Music Network.

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RNA in blood yields picture of disease, fetal development

By Krista Conger

Recent research has shown that tiny fragments of DNA circulating in a person’s blood can allow scientists to monitor cancer growth and even get a sneak peek into a developing fetus’ gene sequences. But isolating and sequencing these bits of genetic material renders little information about how that DNA is used to generate the dizzying array of cells, tissues and biological processes that define our bodies and our lives.

Now researchers at Stanford have moved beyond relying on DNA markers excised from the genes and focusing on RNA sequences in the blood. Instead, they’ve generated a much more dynamic picture by monitoring changing levels of RNA from different genetic material — RNA — in the blood. It’s the biological difference between a still photo and a video when it comes to figuring out what the body is doing moment to moment.

“We think of this technique as a kind of ‘molecular stethoscope’,” said Stephen Quake, PhD, professor of bioengineering and a Howard Hughes Medical Institute investigator. “It’s really only useful for any tissue you care to analyze. There are many potential practical applications for this work. We could potentially use it to look for things going wrong in pregnancy, like pre-eclampsia or signs of preterm birth. And we hope to use it to track general health issues in various organs.”

Keen to have his colleagues combined the use of high-throughput methods of microarrays and next-genera- tion sequencing to analyze the sequences and relative levels of RNA in the blood of pregnant women, healthy volunteers and Alzheimer’s patients. By focusing, on RNA messages encoding proteins known to be pro- duced only in certain tissues, they were able to track the development or health of particular organs throughout the body.

The Lee Otterson Professor in the School of Engi- neering and a Howard Hughes Medical Institute inves- tigator, Quake is the senior author of a paper describing the research published online May 5 in the Proceedings of the National Academy of Sciences. Graduate students Winston Koh and Wenying Pan are lead authors of the paper.

Cellular workhorses

With a few exceptions, your genome, encoded by your DNA, is in every cell in your body. Specific tis- sues and organs are formed by expressing only certain subsets of genes from the thousands of options in your genome. This process is accomplished in part through molecules called messenger RNAs, which carry instructions encoded in genes to the cell’s protein-mak- ing factories. The proteins in turn do much of the work of the cell.

Specialized proteins and other regulatory molecules in each cell control which genes are expressed, when they are expressed and how much of each RNA message is made. As a result, the particular sequences of mes- senger RNA used can vary widely among tissues and between individuals and environmental conditions.

It’s been known for decades that blood contains minute amounts of free-floating RNA — RNA in blood and RNA in dam- aged cells throughout the body. Often this cell death represents natural cellular turnover or the result of disease processes. But, until recently, analyzing this genetic material has been difficult due to its scarcity.

New sequencing techniques capable of handling very tiny amounts of genetic mate- rial are opening broader vistas for research. Scientists are beginning to focus on analyzing the DNA in the blood, either to determine its sequence or to compare the relative amounts of certain chromo- somes. These techniques have applications in diagnos- ing cancers by looking for particular mutations not present in the patient’s genome. Quake’s lab pioneered an approach that allows clinicians to determine whether a patient’s cancer is likely to have conditions such as Down syn- drome that are defined by abnormal chromosomal copy numbers. It is estimated that in 2013, more than 1,000 pregnant women used a version of Quake’s noninvasive prenatal test to learn more about the health of their fetuses.

Tracing fetal tissue development

In the new study, the researchers used a technique previously developed in Quake’s lab to identify which RNA molecules were produced by a pregnant woman likely to have come from her fetus, and which were from her own organs.

They found they were able to trace the development of specific tissues, including the fetal brain and liver, as well as the placenta, during the three trimesters of pregnancy simply by上报ing blood samples from the pregnant women over time.

Quake and his colleagues believe the technique could also be broadly useful as a diagnostic tool by detecting distress signals from diseased organs, perhaps even be- fore any clinical symptoms are apparent. In particular, they found they could detect elevated levels of neurotrophic factors — molecules that help specific RNA messages in people with Alzheimer’s disease as compared with those who didn’t.

Than double the mortality rate of those who died within eight years.

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Quake and his colleagues believe the technique could also be broadly useful as a diagnostic tool by detecting distress signals from diseased organs, perhaps even be- fore any clinical symptoms are apparent. In particular, they found they could detect elevated levels of neurotrophic factors — molecules that help specific RNA messages in people with Alzheimer’s disease as compared with the healthy participants.

Finally, in addition to monitoring messenger RNA levels, which encode protein-making instructions, the researchers were also able to detect other types of RNA — such as long, noncoding RNA and circular RNA — that help the cell to play significant regulatory roles within the cell. Further analysis of these molecules could yield additional insight into health and disease.

“We’ve moved beyond just detecting gene sequences to really analyzing and un- derstanding patterns of gene activity,” said Quake. “Knowing the DNA sequence of a gene in the blood has been shown to be useful in a few specific cases, like cancer, pregnancy and organ transplantation. Analyzing the RNA enables a much broader perspective of what’s going on in the body at any particular time.”

Other Stanford co-authors of the study are postdoc- toral scholar and clinical investigator Charles Gawad, MD; former postdoctoral scholar Christina Fan, PhD; assistant professor of neurology and neuroscience Geoffrey Kremer, MD, PhD; professor of neuro- urology and neurological sciences Tony Wyss-Coray, PhD; assistant professor of obstetrics and gynecology Tair Blumenfeld, MD; and professor of pediatrics and of surgery Yasser El-Sayyed, MD.

The research was supported in part by the March of Dimes and a fellowship from Singapore’s Agency for Science, Technology and Research.

The work was also supported by the Department of Bioengineering, which is jointly operated by the School of Engineering and the School of Medicine.
Diabetic
continued from page 1

the sugar level was trending upward. This occurred without waking the patient. The shunts reduced the cumulative time patients spent with low blood sugars during sleep by 81 percent, with only a minimal increase in nighttime blood glucose levels.

“A system like this should dramatically decrease diabetics’ risk of having a seizure overnight,” said Bruce Buckingham, MD, professor of pediatric endocrinology at Stanford, who led the trial and is a co-author of the study. “Patients and parents will be able to have a better night’s sleep, knowing that there is a much lower risk of severe hypoglycemia at night.” Buckingham is also a pediatric endocrinologist at Lucile Packard Children’s Hospital Stanford.

Diabetics who use insulin pumps usually receive a low dose of insulin throughout the night; it is delivered by the pump through a small catheter inserted under the skin.

In the past, researchers have tried other approaches to prevent low blood sugar during sleep, such as having glucose sensors trigger an alarm for a low blood-sugar level. This has only been partly successful because patients sleep through about 70 percent of the alarms. Since a person with diabetes would shut off their insulin pump if they had a low blood glucose, the next approach was to use the sensors’ glucose values to suspend insulin delivery when the sugar level was trending upward. This occurred without waking the patient.

Each night, the algorithm on the computer was run based on data from the patient’s blood sugar and insulin levels throughout the night. If the algorithm predicted that the blood sugar was likely to drop below a certain level, the insulin pump would be turned off for a period of time.

The new study involved 45 people, ages 15-45, with type-1 diabetes. Each person participated for about 42 nights, for a total of 1,912 nights. The patients slept in their own homes. Both the insulin pumps and the glucose monitors were wirelessly connected to a laptop computer near their beds.

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Laura Roberts receives Distinguished Service Award from American Psychiatric Association

Laura Roberts, MD, professor and chair of psychiatry and behavioral sciences, has received a 2014 Distinguished Service Award from the American Psychiatric Association.

Established in 1964 by the association’s board of trustees, the award honors organizations and individuals that have contributed to the field of psychiatry. Roberts, who is also the Katharine Dexter McCormick and Stanley McCormick Memorial Professor in the School of Medicine, is best known for her work on ethical issues and public policy relating to both clinical care and research science.

Her research has been praised for providing valuable evidence to help resolve complex and controversial issues in health policy related to vulnerable populations. Since 2003, she has been editor-in-chief of Academic Psychiatry, a journal focused on education, mentorship and leadership in academic psychiatry.

“This is a great honor for Dr. Roberts and a fitting recognition of her dedication and outstanding contributions to the field,” said Lloyd Minor, MD, dean of the medical school. “All of us at Stanford Medicine are very proud of her achievements.” iSM
People

Three medical students awarded 2014 Soros Fellowships

Three Stanford medical students are among the 30 recipients of the 2014 Paul and Daisy Soros Fellowships for New Americans, which support graduate study for immigrants to the United States and their children. Each of the three Soros Fellows, who were selected from more than 1,200 applicants, will receive as much as $90,000 for tuition and living expenses in support of graduate education.

ROXANA DANESEHJOU is a student in the MD/PhD program. Her parents immigrated to the United States from Tehran in the late 1970s, when the Iranian Revolution was gaining momentum. In 2011–12, she was awarded an fellowship from the Howard Hughes Medical Institute for her work on anticoagu- lant drug development. She now serves as the lead researcher on the Iranian Genome Project, the first project to study Iranian ancestry through whole-genome sequencing. Daneshjou plans to use her fellow- ship award to support her work toward an MD degree and a doctorate in genetics.

DAN FENG, a student in the M.D./Ph.D. program, was born in southern China and moved to the United States in 2007 after she was offered a full scholarship for biomed- ical graduate studies at the University of Pennsylvania. As a graduate student, she made a discovery that sheds light on why people doing shift work have a higher risk of metabolic disorders. The finding was published in Science in 2011. Feng will use his fellow- ship award to support her work toward an MD degree.

JONATHAN TSAI is a student in the M.D./Ph.D. program. His parents emigrated from China in the 1990s and began a success- ful technology company in Silicon Valley, moving to Brussels with his family as a teenager. After graduating with honors from the Cali- fornia Institute of Technology, he was awarded a Ful- bright Fellowship to study human and cancer growth factors at Israel’s Weizmann Institute of Science, result- ing in publications in leading scientific journals. He is studying how drugs and therapeutic molecules, MD, to develop new tools to study blood and solid organ development and regeneration. Tsai will use the fellowship to work toward an MD degree and a doctorate in developmental biology.

Note: These fellowships are funded by the Soros Fund for Education, which has provided more than $1 billion in support to more than 4,000 students worldwide since its inception in 1973. Full details are available at www.soros.org.

About the Soros Fund for Education

The Soros Fund for Education is a private, not-for-profit foundation created in 1973 by the late George Soros to make investments in educational and cultural institutions, programs, and initiatives around the world. The fund’s mission is to open opportunity and expand educational access to all, with a focus on building the capacity of civil society to support democratic and equitable change. For more information, visit www.soros.org.