INSIDE STANFORD MEDICINE

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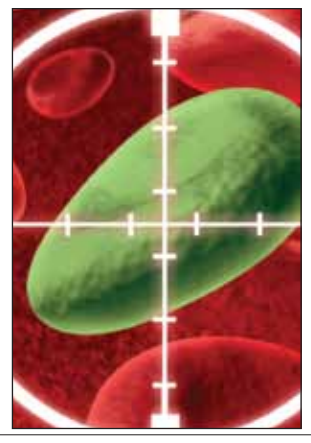

Scientists have found that a discarded drug helps human cells in a lab dish fight off two different viruses.

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After rare procedure, woman can hear her heart beat in another

By Sara Wykes

The first thing Linda Karr asked her doctor after her heart transplant surgery at Stanford Hospital was, "How is my heart donor doing?"

That question is as exceptionally rare as the surgery that made it possible. On Feb. 1, as part of a "domino" procedure, Karr received the heart of Tammy Griffin, who received a new heart and lungs from a deceased donor.

A little more than six weeks later, on March 17, the two women met for the first time. Griffin listened to her old heart beat in Karr's chest as their families and Stanford Medicine doctors looked on. "I feel as though a world of possibilities opens up now for my future — kind of a second chance in life," Karr told Griffin.

"Me, too. I feel the same way," Griffin said.

Karr, 53, See TRANSPLANT, page 6

NORBERT VON DER GROEBEN

Heart-lung recipient Tammy Griffin listens to her old heart beating inside the chest of Linda Karr. They received their new organs in a rare "domino" procedure.

Study: Smokers have a harder time getting jobs

By Jennie Dusheck

A one-year longitudinal study by researchers at the School of Medicine strongly suggests that smokers remain unemployed longer than nonsmokers. And when smokers do find jobs, they earn substantially less than nonsmokers.

The study was published April 11 in *JAMA Internal Medicine*. Judith Prochaska, PhD, MPH, associate professor of medicine, is the lead and senior author.

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Previous studies have demonstrated an association between smoking and unemployment in the United States and Europe, said Prochaska. In an earlier paper, her team found that unemployed job-seekers in California were disproportionately more likely to be smokers than people who had jobs.

Cause or effect of unemployment?

But it has not been clear if smoking is the cause or the result of unemployment. "You don't know if smokers have a harder time finding work or if smokers are more likely to lose their jobs — or that when nonsmokers lose See SMOKING, page 7

Trial of drug for refractory rheumatoid arthritis deemed a success

By Bruce Goldman

In a pivotal phase-3 trial led by a School of Medicine investigator, a novel drug for rheumatoid arthritis substantially reduced symptoms and improved daily physical functioning in patients for whom other therapies had failed.

A study summarizing the 24-week randomized, double-blind, placebo-controlled trial, which was carried out at 178 centers in 24 countries and involved more than 500 adults who had been living with the painful autoimmune condition for 14 years on average, was published in the March 31 issue of *The New England Journal of Medicine*.

"This is the first drug to demonstrate meaningful clinical benefit in patients who've failed virtually every other commercial drug for rheumatoid arthritis," said Mark Genovese, MD, professor of immunology and rheumatology and the study's lead author. The senior author is Josef Smolen, MD, of the Medical University of Vienna, in Austria.

The drug, baricitinib, belongs to a new category of small-molecule drugs, available in pill form, called Janus-kinase inhibitors. They work by interfering with intracellular enzymes whose signaling action is necessary for various inflammatory substances in the body to be effective.

Pain, stiffness and swelling

Rheumatoid arthritis is a progressive, inflammatory autoimmune disease affecting about 1.5 percent of the population of developed countries. It most commonly manifests between the ages of 30 and 60. It causes pain, stiffness, swelling and eventual destruction of multiple joints, typically smaller ones, such as those in the hands and feet. About three of every four people with the disease are women. The reasons for this gender skew are unknown.

HRIANA / SHUTTERSTOCK.COM

Rheumatoid arthritis, which causes pain and swelling in the joints, affects about 1.5 percent of the population of developed nations.

A diagnosis of rheumatoid arthritis once came hand in hand with a bleak prognosis: a greater than 50 percent likelihood of becoming disabled within 20 years. But advances in treating the disorder since the mid-1990s have made for a much-improved outlook, Genovese said. A major innovation, he said, has been the introduction of several kinds of injectable, bioengineered protein drugs, or biologics, beginning in the latter part of that decade.

Three of the eight top-selling drugs in the United States in terms of dollar sales — adalimumab, etanercept and infliximab — are biologics prescribed for rheumatoid arthritis. These three drugs share a common property: They block the action of a substance called tumor necrosis factor, or TNF, secreted by various immune cells, that potently stimulates the immune response and accompanying inflammation. Other biologics prescribed for rheumatoid arthritis — including abatacept, tocilizumab and rituximab, all three of which Genovese See ARTHRITIS, page 6

Greely: Prospect of designer babies raises legal, ethical issues

By Greta Lorge

What if prospective parents were given the opportunity to make decisions ahead of time about the combination of genetic traits their child would inherit?

Stanford law professor Hank Greely, JD, says that's not just a science fiction set-up, but a quandary that future generations will likely face.

The underlying science and technology are advancing rapidly, he noted. Now is the time, Greely believes, to consider carefully "what kind of legal changes would be necessary to try to maximize the benefits and minimize the harm of this new approach to making babies."

The founding director of the Center for Law and the Biosciences and director of the Stanford Program in Neuroscience and Society, Greely studies the legal, ethical and societal implications of emerging biotechnologies. His forthcoming book, *The End of Sex and the Future of Human Reproduction*, envisions a world where procreation may not start in bedrooms, but rather in a petri dish in a medical clinic.

Designer children

Greely describes a scenario: A couple wanting a child would create 100 embryos and receive a DNA dossier for each. This would reveal the presence of genes for serious life-threatening diseases, as well as markers that confer increased risk for less serious conditions. But it also might include genes for physical features, including eye and hair color, height and body type, and markers for behavioral traits, such as athleticism or musical ability. The hopeful parents would then select which embryo to implant based on its expected characteristics.

"Right now, the technology as envisioned in the book is still 20 years away," said Greely, who is also chair of the steering committee for the Stanford Center for Biomedical Ethics. "But there are pieces of it available today."

Pre-implantation genetic diagnosis — which involves extracting a single cell from an embryo created through in vitro fertilization and screening for disease genes or abnormal chromosomes — has been around for 25 years, he said.

However, because it requires egg harvesting for IVF, which is very expensive, Greely expects most couples would not consider pre-implantation genetic diagnosis, or PGD, if they could conceive a healthy child the old-fashioned way.

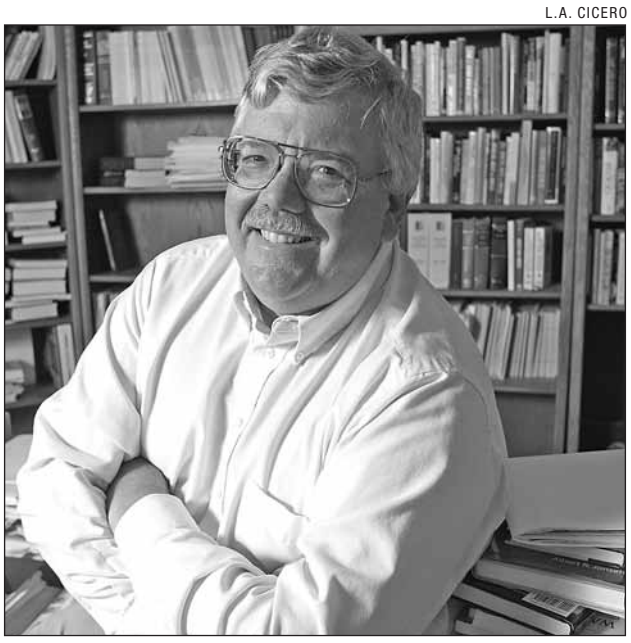
But sooner or later, Greely believes, scientists will succeed in making viable human eggs and sperm from induced pluripotent stem cells derived from skin or other somatic cells.

"And that will be the news story that triggers real interest in what I call 'easy PGD,'" he said. "This will pave the way for a number of new reproductive possibilities. For one, people who are infertile will be able to have their own genetic children. So may same sex couples, since it may well be possible to make eggs from a man's skin cells or sperm from a woman's."

For another, he added, it will eliminate the pressure of a biological clock — at least in terms of conception — allowing women to postpone starting a family.

Yet, by the same token, the ability to make gametes from skin cells might have some undesirable consequences. For example, Greely pointed out that someone could take a paper coffee cup that you casually tossed in the trash and turn you into a parent without your knowledge or consent.

L.A. CICERO



Hank Greely has written a book about the ethical, legal and societal implications of emerging reproduction technologies.

"We probably need some laws to deal with that; unconsenting parenthood seems like a bad idea," Greely said.

Complicated questions

One possibility he proposes would be to require documentation of the provenance of any cells used to derive eggs or sperm.

"I think there are a lot of complicated questions, and for some of them, there is no particular law book to turn to," Greely said.

For example, he suggested, what happens if parents pick an embryo thinking they're getting a boy who will grow up to be like former Stanford quarterback Andrew Luck, but instead when the child grows up, he wants to be poet?

Greely said, "I think, universally, parents are already somewhat surprised by how their children end up. But if you think you've actually picked their genes, will that make you more disappointed? Will that make you sue the clinic?"

Fairness is a central issue, Greely said. What if some people have access to the technology and others don't? He predicts that in rich countries, this child-making process will be subsidized, making it effectively free for prospective parents.

"In part," he said, that will happen "because it will save the health care system a lot of money. You don't need to prevent the births of very many really sick babies to pay for hundreds or thousands of attempts at making babies through easy PGD."

But even so, there will certainly be international disparities, and possibly national ones as well.

People with disabilities

Greely also raises challenging issues with respect to people with disabilities.

"If you've got a genetic disease and this means far fewer people are going to be born with your disease, well, in one sense that's a good thing, but in another sense that lowers the research interest in your disease, the social support for your disease, and it kind of says your society thinks you shouldn't have been born," he said.

Citing the examples of heritable deafness and dwarfism, he noted that it's plausible that parents would want a child like them.

"If a parent deafened a living baby, we'd certainly take the baby away and we'd prosecute the parent," he said. "If parents choose an embryo because it's deaf, like themselves, in order to preserve deaf culture from genocide, what do we do then?"

Greely seeks to spark broad discussions about policies regarding these issues.

"I think something that changes the way we conceive babies affects everyone in such basic ways that it's not a topic that should be left solely to the law professors or to the bioethicists or to the fertility clinics," he said. ISM

This article was commissioned for the spring 2016 issue of Stanford Lawyer *magazine.*

$10 million establishes center to focus on salmonella, immune cell interactions

By Bruce Goldman

A new center at Stanford will focus on understanding the interactions between salmonella bacteria and immune cells infected by the pathogen, as well as on treating such infections.

The Allen Discovery Center at Stanford University for Multiscale Systems Modeling of Macrophage Infection will be headed by Markus Covert, PhD, associate professor of bioengineering. The multidisciplinary center is being funded by a four-year, $10 million grant from the Paul G. Allen Frontiers Group, a nonprofit organization aimed at spurring biomedical innovation. The center could receive $10 million more after that period to fund four more years of work.

The center will integrate cutting-edge modeling, computation and experimental measurements to create multiscale models of the bacteria as they infect human immune cells, shedding new light on how this complex system of cell behaviors creates infectious disease.

Markus Covert

Species of salmonella cause more than 100 million symptomatic infections annually, including 16 million to 20 million cases of typhoid fever. The microorganism's modus operandi is to infect and hide out in immune cells called macrophages, manipulating the metabolism of these cells to its own benefit.

"We are grateful for the recognition and support of Stanford's faculty in the area of quantitative bioscience," said Stanford University President John Hennessy, PhD. "The application of engineering and computational techniques to solving the hardest problems in biomedicine is one of the most exciting and promising research directions."

Denise Monack, PhD, associate professor of microbiology and immunology, and K.C. Huang, PhD, associate professor of bioengineering and of microbiology and immunology, are co-investigators at the center, Covert said.

"We've assembled a unique team with the experience to bring the latest biological and bioengineering knowledge together with industrial-scale computational methods," said Covert, whose research concentrates on building computational models of complex biological processes and using these models to guide experimentation. "We expect that the resulting multicellular modeling platform, which will be available to everyone, will transform the rate at which biological discovery occurs in many areas of bioscience, well beyond infectious diseases."

The Department of Bioengineering is jointly operated by the School of Medicine and the School of Engineering. ISM

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STANFORD MEDICINE

Trial determines that paper tape can help prevent foot blisters

By Tracie White

Ten years ago, Grant Lipman, MD, an emergency medicine physician, was working as a doctor for endurance athletes who were running 25 to 50 miles a day in various parts of the world, from China to Antarctica to Chile.

Despite the harsh conditions and extreme exercise, the most common complaint that Lipman heard from the athletes was about the pain and debilitation caused by foot blisters, the same kind that plagues lots of people, from hikers to women in heels.

"What I kept hearing was, 'Doctor, I'd be doing so well, if only for my feet,'" said Lipman, clinical associate professor of emergency medicine. "Their feet were getting decimated."

Multiple methods of blister prevention have been tried, Lipman said, including powders, antiperspirants, lubricants, tapes and adhesive pads. But despite the numerous scientific studies on blister prevention over the years, there is little evidence to show that any of these methods work well, he said, until now.

Paper tape: Who knew?

In a new study, Lipman and colleagues report that inexpensive paper tape, the kind available at most drugstores, when applied to blister-prone areas prior to exercise, successfully reduced the incidence of foot blisters in those areas. The tape, commonly referred to as surgical tape, is used for wound treatment. It is only mildly adhesive — an advantage because it doesn't tear the blisters if they do occur. The results were published online April 11 in the *Clinical Journal of Sport Medicine*.

"People have been doing studies on blister prevention for 30 or 40 years and never found anything easy that works," said Lipman, who is the lead author of the study. "I wanted to look at this critically." The senior author of the study is Brian Krabak, MD, MBA, a sports medicine physician affiliated with the University of Washington.

> "It's kind of a ridiculously cheap, easy method of blister prevention."

Over the years, in addition to the complaints from the extreme runners, Lipman has heard from military doctors, bemoaning the state of their military recruits' feet. Blisters were keeping recruits from participating in basic training. From his experience treating athletes and listening to his patients, Lipman drew anecdotal evidence that the paper tape method could provide the best answer. Then he set out to test the hypothesis.

155-mile experiment

In 2014, Lipman and his colleagues recruited 128 runners participating in the 155-mile, six-stage RacingThePlanet ultramarathon event that crosses deserts around the globe, including the Gobi Desert and deserts in Jordan and Madagascar.

Paper tape was applied to just one of each of the runners' feet. The untaped areas of the same foot served as a control. (Which foot got the tape and which didn't was chosen at random). The tape was applied by trained medical assistants to either the participants' blister-prone areas or, if they had no blister history, to randomly selected locations on the foot.

The paper tape was applied in a smooth, single layer before the race and at subsequent stages of the race, Lipman said.

The medical assistants followed the runners for 155 miles over seven days.

For 98 of the 128 runners, no blisters formed where the tape had been applied, whereas 81 of the 128 got blisters in untaped areas.

COURTESY OF GRANT LIPMAN

Grant Lipman attends to a blister during an endurance race in the Atacama Desert in Chile.

"It's kind of a ridiculously cheap, easy method of blister prevention," Lipman said. "You can get it anywhere. A little roll costs about 69 cents, and that should last a year or two."

He added, "The best way to make it to the finish line is by taking care of your feet."

Other Stanford co-authors are former wilderness medicine fellows Louis Sharp, MD, Katherine Shea, MD, and Mark Christensen, MD; and Alexandra DiTullio, MD, emergency medicine resident.

The study was supported by a 2014 RacingThePlanet research grant. The preventive taping technique described in the study is discussed in Lipman's book *The Wilderness First Aid Handbook* and a related app, a link to which is available at http://wildernessaid.com.

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

Neanderthal Y chromosome genes likely extinct in modern men, study finds

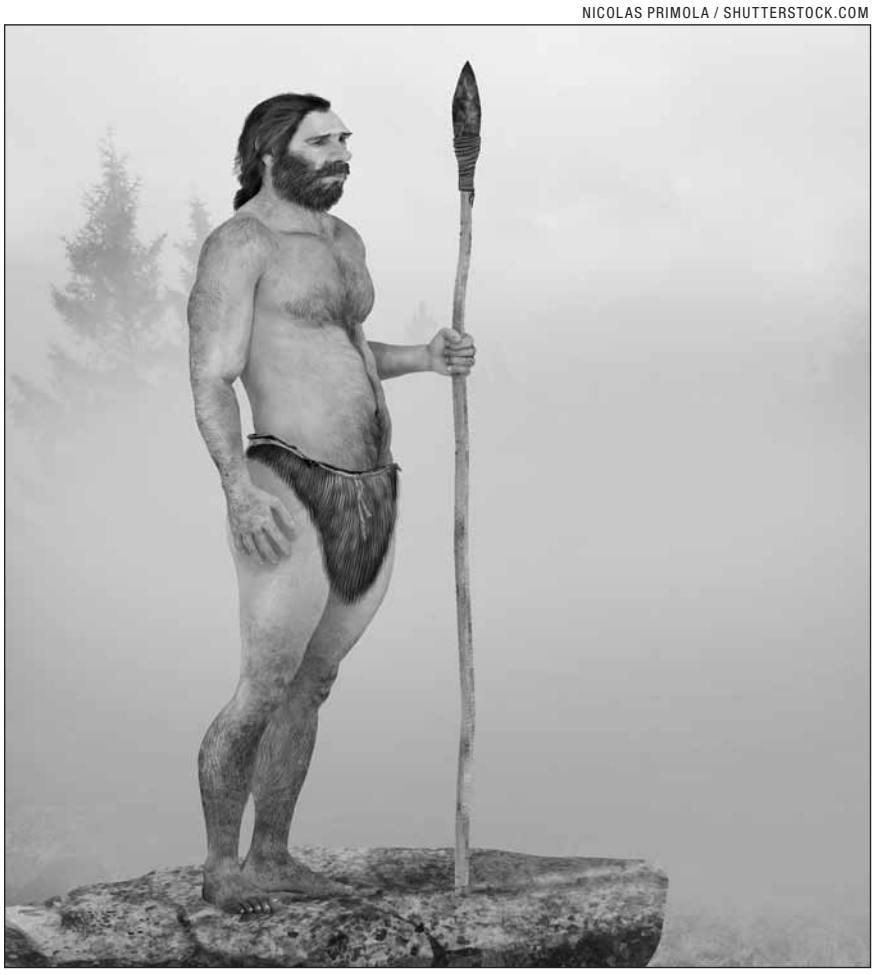
By Jennie Dusheck

Although it's widely known that modern humans carry traces of Neanderthal DNA, a new international study led by researchers at the School of Medicine suggests that Neanderthal Y chromosome genes disappeared from the human genome long ago.

The study was published April 7 in *The American Journal of Human Genetics*, in English and in Spanish, and is available to view for free. The senior author is Carlos Bustamante, PhD, professor of biomedical data science and of genetics at the School of Medicine, and the lead author is Fernando Mendez, PhD, a postdoctoral scholar at Stanford.

The Y chromosome is one of two human sex chromosomes. Unlike the X chromosome, the Y chromosome is passed exclusively from father to son. This is the first study to examine a Neanderthal Y chromosome, Mendez said. Previous studies sequenced DNA from the fossils of Neanderthal women or from mitochondrial DNA, which is passed to children of either sex from their mother.

NICOLAS PRIMOLA / SHUTTERSTOCK.COM



DNA from the Neanderthal Y chromosome, which is passed from father to son, is likely extinct. Scientists believe Neanderthals died out about 40,000 years ago.

Other research has shown that the DNA of modern humans is from 2.5 to 4 percent Neanderthal DNA, a legacy of breeding between modern humans and Neanderthals about 50,000 years ago. As a result, the team was excited to find that, unlike other kinds of DNA, the Neanderthal Y chromosome DNA was apparently not passed to modern humans during this time.

"We've never observed the Neanderthal Y chromosome DNA in any human sample ever tested," Bustamante said. "That doesn't prove it's totally extinct, but it likely is."

Why no Neanderthal DNA?

Why is not yet clear. The Neanderthal Y chromosome genes could have simply drifted out of the human gene pool by chance over the millennia. Another possibility, said Mendez, is that Neanderthal Y chromosomes include genes that are incompatible with other human genes, and he and his colleagues have found evidence supporting this idea. Indeed, one of the Y chromosome genes that differ in Neanderthals has previously been implicated in transplant rejection when males donate organs to females.

Carlos Bustamante

"The functional nature of the mutations we found," said Bustamante, "suggests to us that Neanderthal Y chromosome sequences may have played a role in barriers to gene flow, but we need to do experiments to demonstrate this and are working to plan these now."

Several Neanderthal Y chromosome genes that differ from those in humans function as part of the immune system. Three are "minor histocompatibility antigens," or H-Y genes, which resemble the HLA antigens that transplant surgeons check to make sure that organ donors and organ recipients have similar immune profiles. Because these Neanderthal antigen genes are on the Y chromosome, they are specific to males.

Theoretically, said Mendez, a woman's immune system might attack a male fetus carrying Neanderthal H-Y genes. If women consistently miscarried male babies carrying Neanderthal Y chromosomes, that would explain its absence in modern humans. So far this is just a hypothesis, but the immune systems of modern women are known to sometimes react to male offspring when there's genetic incompatibility.

When did we part ways?

The Y chromosome data also shed new light on the timeline for the divergence of humans and Neanderthals. The human lineage diverged from other apes over several million years, ending as late as 4 million years ago. After the final split from other apes, the human lineage branched into a series of different types of humans, including separate lineages for Neanderthals and what are now modern humans.

Previous estimates based on mitochondrial DNA put the divergence of the **See NEANDERTHAL, page 8**

Resurrected drug effective against two viruses in lab dish

By Amy Adams

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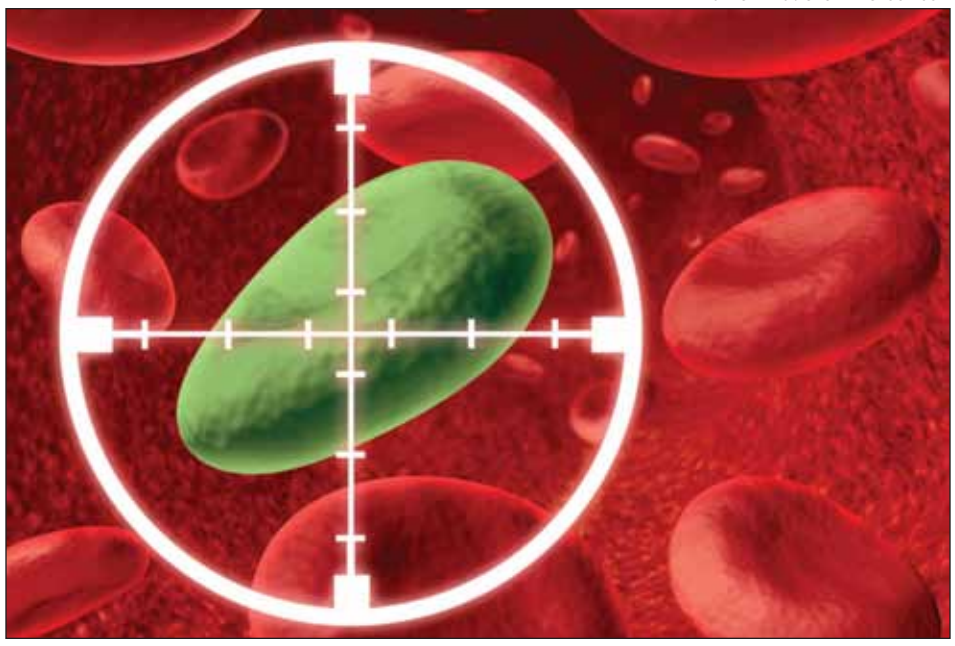


Scientists are working on a drug that targets viruses like Ebola, dengue and Zika, which use RNA rather than DNA as their genetic material.

Viruses have proven to be wily foes. Attempts to fend off viruses causing even the common cold or flu have failed, and new viral outbreaks such as dengue, Ebola or Zika continue to elude drugs.

Given these challenges, a group at Stanford is tackling the problem from a different angle: boosting the human body's ability to resist the virus rather than taking on the virus directly. This approach has paid off with a drug that, in cells in a lab dish at least, helps fight two disease-causing viruses and potentially many more. The work was published March 28 in *Nature Chemical Biology*.

Chaitan Khosla, PhD, a professor of chemistry and of chemical engineering who was one of the senior authors of the paper, said the way the drug works suggests that it could be broadly effective against viruses that use RNA rather than DNA as their genetic material.

"Most of the really nasty viruses use RNA," Khosla said, including Ebola, dengue, Zika and Venezuelan equine encephalitis virus, or VEEV, a mosquito-borne virus that infects horses but can also kill people.

Khosla cautioned that at this stage the team has only shown that the drug is effective in a lab dish and on certain viruses. They plan to test their strategy in animals next to learn whether it is safe and to understand which viral diseases it is most effective against.

A new strategy

This project came about when Jeffrey Glenn, MD, PhD, associate professor of medicine and of microbiology and immunology, founded the ViRX@Stanford center through a grant from the National Institute of Allergy and Infectious Diseases in collaboration with Stanford ChEM-H, which Khosla directs. The center's goal is to develop antiviral strategies targeting human cells rather than the virus.

Scientists typically take a "one drug, one bug" approach to fighting viruses. Glenn's center, however, has a goal of "one drug, multiple bugs."

The team had known about a drug being developed by GlaxoSmithKline that appeared to work along these lines, helping human cells fight viruses. However, after a few initial publications the drug got shelved. Khosla thought that with the help of collaborations formed through Glenn's new center, it might be possible to understand the drug's mechanism and possibly improve upon it, resurrecting the drug from the shelves and delivering it to patients.

Chemistry graduate student Richard Deans started testing that drug on human cells in a lab dish and found that it enabled the cells to fight off viruses that cause either dengue or VEEV, both of which normally kill the cells. These viruses were chosen because they represent a serious threat to human health, and also represent two different classes of RNA viruses and would test the drug's breadth, according to Jan Carette, PhD, assistant professor of microbiology and immunology and an author of the paper.

Chaitan Khosla

Michael Bassik

Although the drug was effective at fighting the viruses, Deans found that over time the drug also caused the human cells to stop dividing.

Unexpected insights

As a first step to improving on the drug, Deans needed to figure out how it worked. For that, he turned to Michael Bassik, PhD, assistant professor of genetics and a senior author of the paper.

Bassik, who is also member of Stanford Bio-X and ChEM-H, had developed a powerful new way of screening every gene in a cell to identify which proteins those genes produce to carry out a particular behavior, like responding to a drug.

From this screen, the team learned that the drug interferes with a protein that is crucial for making the individual building blocks of RNA, the genetic code for the virus. Without RNA the virus can't make more of itself, which explains why the drug was so effective.

However, because of the way the screen was designed, it also revealed two important additional details that the team wouldn't have otherwise known: why the drug doesn't work perfectly and why it causes cells to stop dividing. That information gave the team a way of reducing the drug's side effects and also suggested a way of making it more effective.

"The genome-wide screen carried out in the Bassik lab was really powerful, because it gave us insights into future research strategies," said Deans, who is the lead author of the paper. "I think going forward his strategy will be much more heavily used."

Cells also need RNA, and can get RNA building blocks in two ways — by making them or by importing them from the bloodstream. The drug blocked the cell's ability to make the RNA building blocks but left intact the cell's ability to import them. Without disrupting both pathways, some RNA precursors made it into the cell and were available to the virus.

Ayşe Ökesli, a joint postdoctoral fellow in the Bassik and Khosla labs, said the team is now testing their drug along with another one that is known to block the import pathway to see if the combination is more effective than one drug alone, and to be sure human cells aren't damaged by the absence of RNA building blocks.

Less toxic

Knowing how the drug worked also explained why it caused the body's normal, healthy cells to stop dividing. The same building blocks needed for RNA synthesis are also needed to make DNA, the cell's genetic code that it replicates with each division to carry out business as usual. When a cell runs out of DNA building blocks, it can no longer divide.

Knowing the problem, the team could devise a solution. They fed the cells a slightly different building block that can only be used to generate DNA, not RNA. With that added to the mix, the cells successfully fought off both dengue and VEEV and were able to keep dividing normally. This knowledge could help make the drug less toxic in animals and eventually people.

Khosla said they plan to test the drug combination against many different RNA viruses to learn which it fights most effectively. If the drug combination is successful in animals, they hope it might become among the first broad antiviral strategies for human disease.

The research was funded by the National Science Foundation Graduate Research Fellowship, a Burt and Deedee McMurtry Stanford Graduate Fellowship, the National Institutes of Health, an NIH Director's New Innovator Award Program and a seed grant from Stanford ChEM-H. ISM

Tracking pain: How health data provided by patients improves care

By Lindzi Wessel

Fifteen years ago, when professor of anesthesiology Sean Mackey, MD, PhD, began working in pain medicine, he found himself hampered by the lack of data available for each patient.

"Physicians go through a very laborious, very frustrating, trial-and-error process," he said. That's particularly true when treating chronic pain, where doctors need information on patients' social and emotional well-being, as well as their physical symptoms.

Long-term pain can shift the behavior of the nervous, immune and inflammatory systems in ways that are challenging to predict or track. Loss of physical function can damage a patient's ability to function socially. It's easy for patients to get depressed, anxious and angry. Assessing all of these factors is crucial to recovery, but the data can be overwhelming for patients to provide and for physicians to assimilate.

Streams of data

"I used to pay high school students to scan pen-and-paper patient surveys over the weekend," said Mackey, who holds the Redlich Professorship. "The surveys took 45 minutes for patients to fill out, and we couldn't use the information in real time."

So Mackey and his colleagues created a computer-based system that uses streams of data from many patients to help physicians provide the best care for individuals. "It has utterly changed the way we practice medicine at Stanford," he said.

The system, first used in 2012 in the Stanford Pain Management Center, adapts questionnaires as patients fill them in, skipping irrelevant questions and, as a result, speeding up the process. It also creates graphs displaying the patient's progress in various categories so both the doctor and patient can see it. More recently, the team has begun entering patients' genetic information, as well.

The program, called the Collaborative Health Outcomes Information Registry, has since been adopted by other Stanford Medicine clinics and now contains data from about 10,000 people. Physicians can use the data to analyze why some patients improve faster **See CHOIR, page 5**

JASON HOLLEY

Magnet-powered bone-lengthening device reduces pain, infection risk

By Erin Digitale

Orthopedic surgeons have developed a new device that reduces the pain, scarring and infection risk associated with lengthening a leg bone. It replaces an external brace, which must be attached outside the leg using pins through the skin, with a sleek, magnet-powered telescoping rod that is bolted entirely inside the bone.

"This device is a big step forward for kids with discrepant leg lengths," said Scott Hoffinger, MD, an orthopedic surgeon with Stanford Children's Health and clinical assistant professor at the School of Medicine. He has used the device in treating seven patients, including the first child in Northern California to receive it.

To lengthen a bone, a surgeon saws crosswise through it and braces the sawed ends 1 millimeter apart. The body grows new bone into the gap. With both the old and new devices, the patient adjusts the brace to move the bone ends half a millimeter further apart, twice a day, until the bone reaches the desired length. Bracing continues until the bone has hardened.

Now, instead of pinning a patient's leg into a bulky external brace, surgeons can accomplish the same thing by placing a small telescoping rod inside the bone's shaft to brace and extend it. The implant contains a magnet-powered motor. The patient holds a magnetic field generator against the leg, which powers the motor inside the implant, for twice-daily, six-minute lengthening sessions.

Causes of leg-length discrepancies

"The biggest advantage is that we can lengthen a child's bone without having to pierce his or her skin and muscles for months with an external fixator," Hoffinger said. "It's more comfortable for the patient both physically and psychologically to avoid having a big frame outside their leg with pins going through to the bone."

The external frame is still required in cases where a leg bone needs straightening, such as when a child's foot is aligned at the wrong angle. However, the new, magnet-powered internal device will work for most children with different-length legs.

Leg-length discrepancies can occur because of congenital conditions that cause problems in bone growth, fractures that heal crookedly, and tumors or blood vessel disorders that affect the bone's growth plates.

Perhaps no one better understands the advantages of the magnetic implant than 18-year-old Andrew Hirsch, one of the few patients to have had his leg bones extended using both the old and new techniques. Andrew was born with fibular hemimelia, a disease that caused his right leg to be shorter than his left and to grow very slowly. He had the old-style external fixator used to lengthen the leg's lower bones by almost 3 inches in 2010, when he was 13. But a few years later, after a growth spurt, his legs were again uneven. By then, Hoffinger had begun using the internal device in other patients and thought it would be a good fit for Andrew's needs. In 2014, at Stanford Children's Health Specialty Services-Emeryville, he explained to Andrew how the new technology could add more than an inch to his right femur. "I was amazed about how much the technology for this kind of stuff had evolved in four years," Andrew said.

X marks the spot

When Andrew's lower leg was lengthened with the old, external fixator, the process was slow and painful. The pins going through his skin and muscle tugged with every bend of his knee, and his ankle and foot were immobilized in a gigantic horseshoe-shaped brace. The pin sites were prone to infection. Lengthening took three months, and he was on crutches for another three months while his new bone hardened. The fixator required four surgeries to remove. Andrew missed a lot of school and his favorite sports: baseball, competitive swimming, skateboarding and water polo.

When his femur, the upper-leg bone, was lengthened with the internal rod, everything was different.

"The fact that there was nothing on the outside of his leg after he recovered from the initial surgery was huge," said Andrew's mom, Luann Hirsch. "It really saved us a lot of hassle, because we battled infections the entire time with the external device."

Instead of the wrenches he had used to expand his external brace, with the magnetic implant, "I had a little 'X' drawn with Sharpie on my leg, placed the external magnet on top of it, flipped a couple of switches, and grew half a millimeter twice a day," Andrew said. "And the pain was way more low-key."

'Wispy layers of bone'

His right femur was lengthened 37 millimeters, almost an inch and a half, requiring five weeks of twice-daily adjustments. Because the rod that holds the magnet is quite strong, Andrew didn't have to wait for the new bone to harden to begin using it; instead, he could walk on his right leg soon after the 37-day lengthening process was complete.

"When we X-rayed Andrew's leg during the process, we saw a gap between the two ends of the bone, the rod inside the bone, and wispy layers of bone being formed around the rod, maturing and getting solid," Hoffinger said.

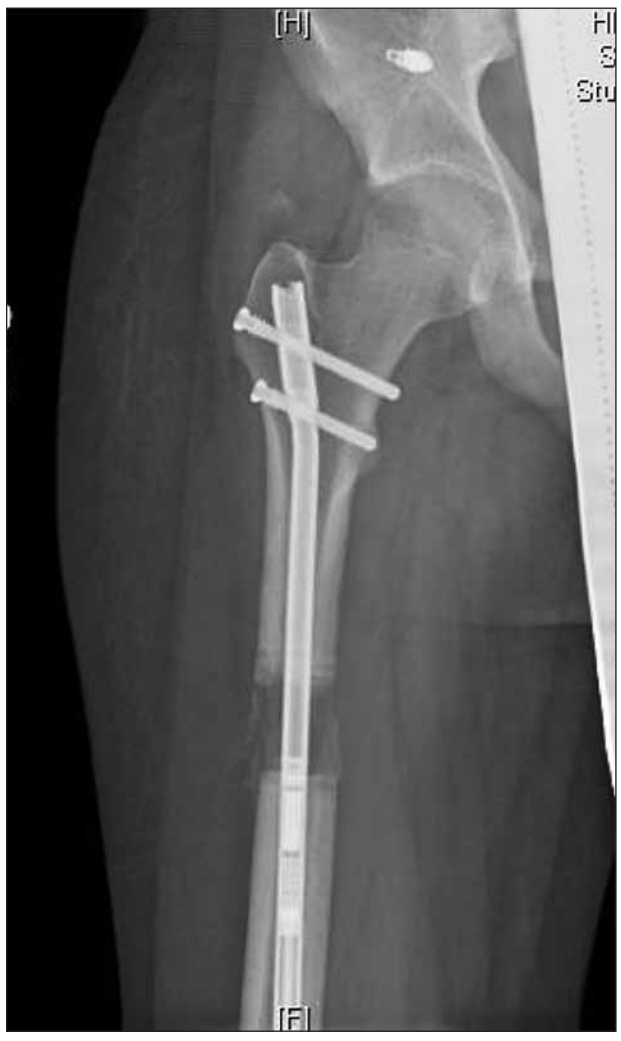
The magnetic motor in Andrew's leg was removed Jan. 21 at John Muir Medical Center in Walnut Creek. (Stanford Children's Health and John Muir Health are partners in bringing comprehensive children's specialty services closer to home for families in Contra Costa County and surrounding communities.) Hirsch said it was her son's easiest journey to the operating room yet: The set of three simple procedures was completed in one day and required only a one-night hospital stay. He was walking again three days later, and Hoffinger said everything looked good when he saw Andrew for his follow-up visit at Stanford Children's Health Specialty Services-Walnut Creek.

The magnet-powered device will soon help many more kids walk easily, Hoffinger said. "The new magnetic device allows us, as surgeons, to be less disruptive to kids' lives," he said. "Andrew has so many plans for the future. It's great to know that his leg won't be holding him back." ISM

NORBERT VON DER GROEBEN

Andrew Hirsch checks in with his surgeon, Scott Hoffinger, after using a magnet-powered telescoping rod to lengthen the bone in his upper leg.

LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD



An X-ray shows the rod implanted in Hirsch's leg. The device helped add more than an inch of bone to his right femur.

CHOIR

continued from page 4

than others and what makes patients vulnerable to complications like depression or addiction to painkillers. The CHOIR team is using it to see which patients are most likely to be dissatisfied with their health-care services, then ensure these patients get more attention.

Stanford's Division of Pain Management and the Center for Clinical Informatics developed CHOIR with support from the National Institutes of Health and the Redlich Pain Endowment. Mackey is sharing the software, which is open-source, nationwide.

'The future of health care'

"The goal is to create a sharing ecosystem of modules," said Mackey. The University of Florida has created a module to integrate CHOIR data into electronic medical records, and the Medical College of Wisconsin has contributed one that sends patients reminders using SMS texting. Ming-Chih Kao, MD, PhD, a Stanford clinical assistant professor of anesthesiology and of orthopedics, has developed several modules that together reduce the time physicians spend on the computer and increase time spent with patients.

"The vast majority of challenging medical conditions that we're facing now and into the future are chronic diseases," said Mackey. He said a shift to medical care aided by masses of health information provided by patients may be the most effective way to help those who are chronically ill. CHOIR is a powerful tool to accomplish this, he said.

"This is the future of health care," says Mackey. "What is novel now at Stanford is going to be commonplace in five to 10 years." ISM

60 Minutes correspondent Lesley Stahl to discuss longevity and aging April 26

Lesley Stahl

Broadcast journalist Lesley Stahl and Stanford psychologist Laura Carstensen, PhD, will discuss aging and longevity at a Stanford Health Policy Forum from 1-2 p.m. April 26 at the Li Ka Shing Center for Learning and Knowledge.

The program, titled "Longevity: The benefits and burdens of an aging society," will be moderated by Paul Costello, the School of Medicine's chief communications officer, and is free and open to the public.

Stahl, who has been a correspondent for the CBS News program *60 Minutes* for 25 years, recently published a book, *Becoming Grandma*, which investigates the science and joys of grandparenting. Carstensen is the founding director of the Stanford Center on Longevity, the Fairleigh S. Dickinson Jr. Professor in Public Policy and a professor of psychology at Stanford.

The discussion will focus on the widespread societal effects of a surge in the number of elderly individuals.

The Stanford Health Policy Forum is a discussion series sponsored by the medical school's office of the dean. ISM

Transplant

continued from page 1

promised Griffin, 51, that she'd take good care of her new heart, adding, "Even though we were strangers before today, you'll always be part of me."

Donor organs in short supply

Organs available for transplant are in short supply. Heart-lung combinations are even more rare because a set of heart and lungs is usually split up so that the organs can benefit two people instead of just one. Domino transplantation of a heart-lung and heart does, however, benefit two people. A highly unusual procedure, it has only been performed at Stanford eight times before, last in 1994.

For Griffin, who has cystic fibrosis, receiving new lungs was critical. Her lung capacity had diminished so much that she was on oxygen full time, unable to do much at all. She had so little energy that she couldn't get through a shower without sitting down to rest.

Her heart, however, was still functioning well. "Her heart was an innocent bystander pushed out of its normal position in the middle of the lungs as her right lung shrank and the left one expanded," said Joseph Woo, MD, a cardiothoracic surgeon at Stanford Health Care who oversaw and coordinated the surgical teams that conducted the domino procedure. That displacement made a heart-lung transplant the only viable option for Griffin, said Woo, who is also professor and chair of cardiothoracic surgery and the Norman E. Shumway Professor in Cardiovascular Surgery in the School of Medicine.

Getting the calls

Griffin lives in Happy Valley, a town near Portland, Oregon. She was on the phone with her sister the afternoon of Jan. 29 when another call came in. It was a doctor from Stanford, who told her there was a heart-lung donor for her. Griffin and her husband, Jim, started to panic a bit, trying to pack and find a flight. "I thought I was going to lose my chance," she said. Then she received another call to say she didn't have to rush quite so fast. The organs would be waiting for her. The Griffins arrived at Stanford around midnight that day.

Karr, who lives in Berkeley, was diagnosed almost 20 years ago with right ventricular dysplasia, a genetic disease that causes a dangerously abnormal heart rhythm. Over time, it became difficult for her to walk down a hall at work without having to stop and rest, and impossible to walk her dog. Even so, she wasn't very high on the transplant waiting list.

"My doctor told me I'd have to be hospitalized to move up — and if my deterioration was rapid, I might not get a heart in time," she said. Then, on Jan. 30, she turned on her phone after coming out of a movie theater — something she didn't always remember to do, she said — and it rang. It was a Stanford doctor: A possible heart donor had been found, he said, and someone would call back in four hours. She checked into Stanford Hospital the following day.

NORBERT VON DER GROEBEN

Joseph Woo oversaw and coordinated the surgical teams that conducted the domino procedure.

Other Stanford Medicine physicians, including Michael Fowler, MD, director of the Heart Failure Program, and Gundeep Dhillon, MD, medical director of the Heart-Lung and Lung Transplantation Program, provided pre-transplant care to Griffin and Karr and are providing post-transplant care to them, as well.

"The extraordinary work of Dr. Woo and his team demonstrates the very best of an academic medical center — where our research informs the development of revolutionary treatments like the domino procedure, which we then use to save the lives of our patients," said Lloyd Minor, MD, the Carl and Elizabeth Naumann Dean of the School of Medicine.

'I am optimistic'

Karr is making good progress toward recovery. She's started participating in a cardiac rehabilitation class, and she's hoping to be able to again to run a 10K, ride a mountain bike or even just jog. "I would be thrilled just to ride my bike up an incline without having to get off and push it," she said. "When I think about my future, I am optimistic."

Griffin is progressing in her recovery, too. "Now I can walk and talk at the same time," she said. For the first time in more than two years, she said, she was able to walk with her husband on a beach.

Their son Austin Griffin, who was just 10 when his mother's condition began to deteriorate, is a college student now, determined to be a doctor — a lung specialist so he can help people like her, his mother said.

Knowing that she was able to help someone else gives Tammy Griffin great joy. "I didn't want my heart thrown away," she said, "and I thought, I'll be able to meet the person who has my heart! How many people can say that?"

"We hope this story will raise awareness how scarce organs are," said Woo. "People are waiting and dying on those transplant lists. We would like to see that change."

What surgeon Jack Boyd, MD, said he will especially remember from the domino procedure was one particular moment. Boyd, a clinical assistant professor of cardiothoracic surgery who has been at Stanford for about a year and a half, led the team that transplanted Griffin's heart to Karr. Once the heart was sutured into place, blood flow through the aorta was restored. "Sometimes hearts don't start up on their own, but in Karr's case, Griffin's heart started right up — and in a pretty normal rhythm," he said. "It was truly awesome." ISM

Arthritis

continued from page 1

also played a role in developing — act through different immune-modulatory mechanisms.

The success of the plethora of drugs now used for treating rheumatoid arthritis carries a downside: Increasing numbers of patients become refractory. The drugs they're taking no longer provide sufficient benefit, or they produce unacceptable side effects, or both. As a result, Genovese estimates, some 15 to 20 percent of rheumatoid arthritis patients find themselves in the position of having exhausted the current inventory of available medications.

"It's an ever-growing population," Genovese said.

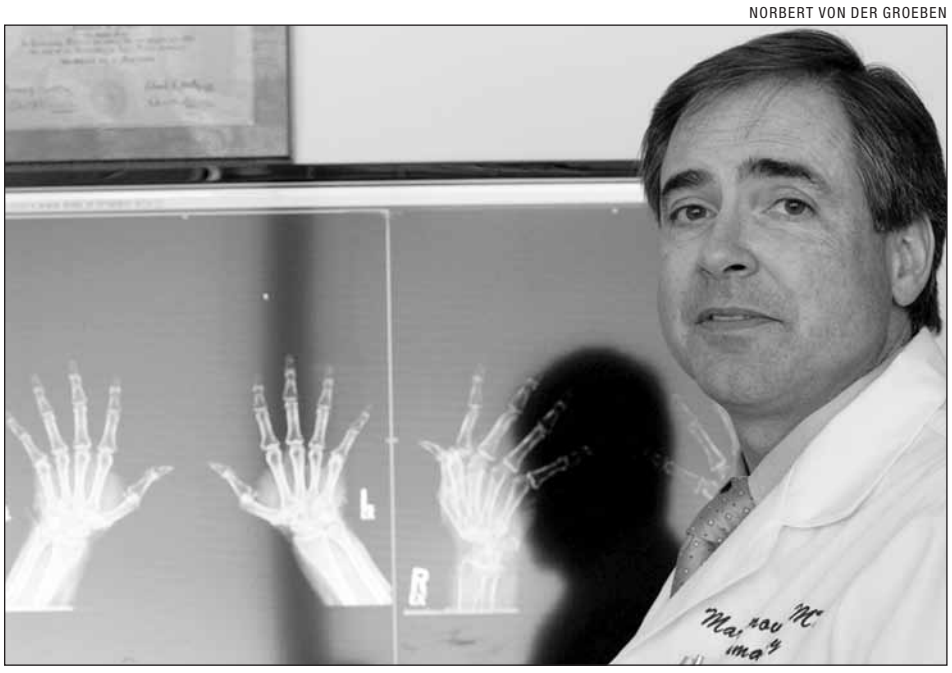
It was these refractory patients who were the focus of the new trial. They had moderate to severe cases of rheumatoid arthritis, with at least six joints affected. All of them had failed at least one anti-TNF biologic, and many had failed two or more.

In addition, the trial included a number of patients who had failed other classes of biologics targeting different sources of immune activation. All patients were currently on other medications for their rheumatoid arthritis.

Reduced symptoms

The 527 patients who participated in the trial were randomly assigned to one of three study arms, where they received once-daily regimens of, respectively, 4 milligrams of baricitinib, 2 milligrams of baricitinib or a placebo for 24 weeks.

NORBERT VON DER GROEBEN



Mark Genovese is the lead author of a study that found that a drug called baricitinib was an effective treatment for rheumatoid arthritis in patients for whom other drugs didn't work.

Some 55 percent of the patients assigned to the higher dose experienced a reduction of at least 20 percent in the number of affected joints at week 12, the primary endpoint of the study. For patients on the lower dose, 49 percent experienced a similar reduction. In contrast, only 27 percent of the patients receiving a placebo saw this effect.

> "The drug worked well across all patient subgroups."

Patients on either dose of baricitinib also had improved physical function and reductions in markers of inflammation, both in absolute terms and in comparison with placebo, the study found.

The improvements in all baricitinib-treated groups largely remained at 24 weeks, said Genovese.

Patients' individual medical histories and prior drug regimens didn't much effect their response to baricitinib treatment, Genovese said. "The drug worked well across all patient subgroups, independently of what they'd been taking before or how long they'd had the disease," he said.

Shingles incidence

Adverse events, most often in the form of mild upper-respiratory infections, as of 24 weeks into the trial were more common among high-dose and low-dose baracitinib recipients — 77 percent and 71 percent, respectively — than among those receiving placebo — 64 percent. Adverse events deemed serious affected 10 percent of the high-dose group, 4 percent of the low-dose group and 7 percent in the placebo group.

At week 12, about 2 percent of patients in the high-dose group, versus 1 percent and 0.5 percent in the low-dose and placebo groups, respectively, had developed herpes zoster, also known as shingles. The disease stems from a reactivation of the latent chicken-pox virus that triggers painful skin eruptions in people whose immune systems have been weakened by, for example, old age or immunosuppressant drugs. At 24 weeks, the corresponding rates were 4 percent, 1 percent and 1 percent.

Baricitinib also appeared to raise both high-density and low-density lipoprotein levels, with unclear clinical implications, Genovese said.

Three other phase-3 trials of baricitinib for rheumatoid arthritis — one in newly diagnosed patients, another head-to-head versus adalimumab and a third for patients for whom a first-line treatment, methotrexate, proved inadequate — have shown that the drug reduces symptoms and prevents structural damage.

The trial was sponsored by Eli Lilly and Co., the manufacturer and licensee of baricitinib.

Lilly has filed for approval of the drug by the U.S. Food and Drug Administration, said Genovese, who noted that he has been serving as a consultant with Lilly and was involved in its successful phase-2 trials of baracitinib for rheumatoid arthritis.

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

OBITUARY

Surgeon Lars Vistnes, who helped found Interplast, dies at 88

By Sara Wykes

Lars Vistnes, MD, who survived the World War II occupation of his hometown and home in Norway to become a nationally recognized pioneer in oculoplastic surgery at Stanford Medicine, died March 28 in San Francisco of an abdominal aneurysm. He was 88.

Vistnes' professional colleagues remembered him for his surgical skills, teaching ability and organizational leadership; his family knew him as patient, gentle and good-natured, despite a years-long struggle against failing eyesight caused by glaucoma. By the time he died, the emeritus professor of plastic surgery was almost completely blind.

Vistnes was born June 22, 1927, in Stavanger, Norway. His mother died when he was 3; his father died shortly thereafter. Older siblings raised him in the family home, which they shared during the war years with German soldiers who arrived after an aerial bombing of the town in 1940.

Medical student and bellboy

Bright and a good student, Vistnes was encouraged by his family to pursue higher education. After he graduated from high school, he went to Canada to live with an older sister and her husband in Saskatchewan so he could attend the university there. He earned a medical degree in 1957 from the University of Manitoba College of Medicine; he met his wife, Carol, while on summer break. "We were both working at the hotel at Lake Louise, near Banff, in the summers," said Carol. "He worked there every summer, mostly as a bellboy — for the great tips — through medical school." He also took advantage of the spectacular mountains that surround the hotel, she said, joining the Alpine Club of Canada and climbing the higher peaks, some of which top 10,000 feet.

After his medical school graduation, Vistnes served for three years as a captain in the Canadian Armed Forces. He arrived at Stanford in 1971, shortly after finishing a six-year residency in general and plastic surgery.

Vistnes was appointed acting assistant professor of surgery at the School of Medicine and chief of plastic and reconstructive surgery at what was then called the Veterans Administration Medical Center in Palo Alto. By 1980, he had become chief and program director of plastic surgery at Stanford; he later served as acting chair of the Department of Surgery. He was co-director of the faculty mentoring program from 1994 until his death.

Lars Vistnes

'A valued mentor'

"Year after year, Dr. Vistnes accepted new leadership challenges and responsibilities," said Vincent Hentz, MD, professor emeritus of surgery, another former chief of the plastic surgery division. "He was instrumental in the development of the Stanford plastic surgery board review course and in the department's evolution to include functional restoration in its mission. There were many retirement parties for him, but he remained a valued mentor at Stanford."

Vistnes was especially known for a treatment he first created for veterans of the Vietnam War. "He found a way to reconstruct eye orbits and eyelids so veterans who had lost an eye in combat could be fitted with an aesthetic prosthetic eye instead of a patch or other poor disguise," Hentz said. Vistnes also created the VA's first oculoplastic clinic, Hentz said, "a clinic that still exists."

Vistnes made other professional marks: He was the editor-in-chief of the *Annals of Plastic Surgery* from 1982 to 1992, and he wrote five books and 24 book chapters on aspects of plastic and reconstructive surgery.

He also served on the boards of the Plastic Surgery Educational Foundation, the American Association of Plastic Surgeons, the California Society of Plastic Surgeons and the American Board of Plastic Surgeons. From 1993 to 2003, Vistnes was a board member of the Glaucoma Research Foundation.

Co-founder of Interplast

Vistnes was also a founding director of Interplast Inc., now known as ReSurge International, the first group to bring advanced reconstructive surgery to children and adults in countries that lacked it. "It was hard work, but he was part of a great team that accomplished rewarding results," said his son, Richard. "The trips were a central part of his life's mission as a doctor." Vistnes made many Interplast trips to Guatemala, Honduras, Peru and Samoa. Most of the medical settings were basic: In Samoa, Vistnes operated in the open air.

He also loved being a father and grandfather. "He liked to show people how to do things," Richard said, "and he loved when the grandkids would come over. My wife remembers how when the kids were babies, if they were crying or fussing, he had this ability to pick one up, say a couple of words and they would just quiet down."

One of those grandchildren, now a college sophomore, said Vistnes had been an important guide throughout his life. "He was often there when I had to make some kind of decision, even when I was really young," Eric Vistnes said. "He was always there to help anyone who asked — and so humble even though he had done so many great things."

In addition to his wife and son Richard, Vistnes is survived by his sons Dean of Redwood City, California, and Greg of Rockville, Maryland, as well as seven grandchildren.

Donations may be made in his memory to the Glaucoma Research Foundation, 251 Post St., Suite 600, San Francisco, CA 94108. ISM

Smoking

continued from page 1

their jobs, they become stressed and start to smoke," said Prochaska.

In a first step toward establishing that smoking may actually prevent people from getting jobs, Prochaska and her team surveyed 131 unemployed smokers and 120 unemployed nonsmokers at the beginning of the study and then at six and 12 months. "We found that smokers had a much harder time finding work than nonsmokers," said Prochaska.

Judith Prochaska

At 12 months, only 27 percent of smokers had found jobs compared with 56 percent of nonsmokers. And among those who had found jobs by 12 months, smokers earned on average $5 less per hour than nonsmokers.

"The health harms of smoking have been established for decades," said Prochaska, "and our study here provides insight into the financial harms of smoking both in terms of lower re-employment success and lower wages."

Prochaska and her colleagues used survey questions and a breath test for carbon monoxide levels to classify job seekers into either daily smokers or nonsmokers. Participants were not randomized, and smokers and nonsmokers differed in a number of important ways besides whether they smoked. For example, smokers were, on average, younger, less-educated and in poorer health than nonsmokers. Such differences might influence job seekers' ability to find work, said Prochaska.

For this reason, the researchers analyzed their data to control for these and other factors, such as duration of unemployment, race and criminal record. "We designed this study's analyses so that the smokers and nonsmokers were as similar as possible in terms of the information we had on their employment records and prospects for employment at baseline," said co-author Michael Baiocchi, PhD, an assistant professor of medicine who oversaw the data analyses.

After controlling for these variables, smokers still remained at a big disadvantage. After 12 months, the re-employment rate of smokers was 24 percent lower than that of nonsmokers.

Testing the hypothesis

In a follow-up study already in progress, Prochaska and her team are testing an intervention that helps job seekers quit smoking. Smokers unemployed no longer than two years are being randomized into one of two groups. Those in the treatment group receive special help to quit smoking, while those in the control group receive brief advice and referral to a help line for quitting smoking. The hypothesis is that those who successfully quit smoking will have an easier time getting hired. The researchers hope to enroll a total of 360 smokers; more than 60 have already enrolled. Residents of the San Francisco Bay Area who are interested in participating in the study can call (415) 216-5853 for more information or go to http://www.employmentsmokingstudy.com.

Other Stanford-affiliated co-authors of the study published April 11 are clinical research coordinator Anne Michalek; postdoctoral scholars Catherine Brown-Johnson, PhD, and Eric Daza, DrPh; and research assistants Nicole Anzai and Amy Chieng.

Researchers from the San Francisco Department of Veterans Affairs and the Buckelew Programs Residential Support Services, in Marin County, also contributed to the study.

The research was supported by the State of California Tobacco-Related Disease Research Program, with a Pilot Community-Academic Research Award; by the National Heart Lung and Blood Institute (grant T32HL007034); and by the Agency for Healthcare Research and Quality.

Stanford's Department of Medicine also supported the work.

Prochaska has provided expert witness testimony in litigation against tobacco companies and consults with Pfizer on smoking cessation medication. ISM

New compounds have potential to combat Lyme disease, study finds

By Becky Bach

When physicians diagnose Lyme disease, they usually prescribe standard antibiotics — and for many patients, that's enough. But for 10 to 20 percent of patients, the disease persists, causing joint paint, neurological difficulties and fatigue, among other symptoms.

New drugs, capable of completely eliminating the disease-causing bacteria *Borrelia burgdorferi* at the onset, are needed. Recently, a team of researchers at the School of Medicine have discovered a few promising leads.

In a study published April 1 in the journal *Drug Design, Development and Therapy*, the researchers tested 4,366 drug compounds for their efficacy against *B. Burgdorferi* in the lab. They picked the top 20, which have all been approved by the U.S. Food and Drug Administration for a variety of uses — one, for example, is used to treat alcohol abuse — and subjected them to additional tests. These compounds blocked the growth of between 95 and 99.8 percent of the bacteria in the samples.

For new cases of Lyme disease

A key caveat: These compounds could be beneficial for those with new cases of Lyme disease. The drugs are not being considered for use for patients who are currently struggling with persistent Lyme symptoms.

"We know the way we treat the patient during the acute period [after infection] is critical. If we treat them with a very effective antibiotic that can kill the bacteria even in the beginning state, we can possibly avoid this 10 to 20 percent of patients who always have the disease," said Jayakumar Rajadas, PhD, senior author of the study and director of the medical school's Biomaterials and Advanced Drug Delivery Laboratory. The lead author is postdoctoral scholar Venkata Raveendra Pothineni, PhD.

Other groups worldwide are striving to improve treatments for Lyme disease. Rajadas attributed the team's preliminary success to access to the equipment, supplies and know-how to develop a new assay capable of quickly identifying the most successful compounds. The team used a technique called high-throughput screening, which rapidly allows researchers to examine hundreds of compounds.

Tests on the compounds are ongoing. "We are trying to take it to the clinic," said Rajadas, who is is also assistant director of the Cardiovascular Pharmacology Division of the Stanford Cardiovascular Institute and is a member of the Lyme Disease Working Group.

Laura Roberts, MD, professor and chair of psychiatry and behavioral sciences at Stanford and co-chair of the Lyme Disease Working Group, lauded the work.

"The use of high-throughput screening to assess candidate compounds is a welcome innovation with important results for new drug development," she said.

Other Stanford co-authors are senior research scientists Dhananjay Wagh, PhD, Mohammed Inayathullah, PhD, and Mansi Parekh, PhD; visiting scholar Mustafeez Mujtaba Babar, PhD; David Solow-Cordero, PhD, director of the Stanford High-Throughput Bioscience Center; postdoctoral scholar Kwang-Min Kim, PhD; and high school student Aneesh Samineni.

The research was supported by the Bay Area Lyme Foundation. BioADD also supported the work.

Pothineni and Rajadas have applied for a patent related to several of the compounds. ISM

Physician chronicles personalized quest for better health

By Kathy Zonana

It was meant as a joke, but it stung. Larry Chu, MD, had just stood up in front of the room at the closing dinner of the first Medicine X conference, a fast-paced, multiday program on emerging technology in medicine for which he is the executive director. He remarked that he hadn't eaten anything all day. A senior faculty member said, "Really, Larry? Because it looks like you could afford to skip a meal."

"I was speechless," said Chu, an associate professor of anesthesiology, whose weight has fluctuated between 200 and 275 pounds over the past 12 years. "Now I can say, 'Go look at my blog. Look at those days I ate 500 calories a day and didn't lose any weight.'"

Chu's blog, precision: me, chronicles the first 90 days of his effort to lose weight and reverse prediabetes. On it, he tracks his weight, lab values, medications, food, exercise and symptoms like hunger and headaches.

"Obesity and weight loss are a very strong case for precision health. We know that one single approach will not work for everyone," he said. Chu and his weight-loss physician, Rami Bailony, MD, of Enara Health, knew Chu had gotten stuck at certain weights in the past, unable to lose any more.

His exercise regimen was solid; he'd been working out with a personal trainer for a decade. And he'd had periodic success with low-carb diets — they curbed his appetite — but he couldn't cease them without regaining weight.

'A demonstration project'

Bailony and Chu thought that Chu's high insulin levels were contributing to his weight gain, and that a very-low-calorie diet would lower them while providing balanced macronutrients. If it didn't work, they'd use what they'd learned to try something else.

Chu believes this type of physician-patient partnership will become increasingly common. "Precision: me is in many ways a demonstration project of how people can participate in precision health care," he said. "Imagine what we could learn if people shared their data the way I'm sharing the data, and we could then pool that data. We'd have a much more detailed and powerful view of obesity."

As fond as he is of data — and this is a man who has strapped a continuous glucose monitor to his leg and named it "Dexy" — Chu also emphasizes the value of storytelling: "Stories add context to the data."

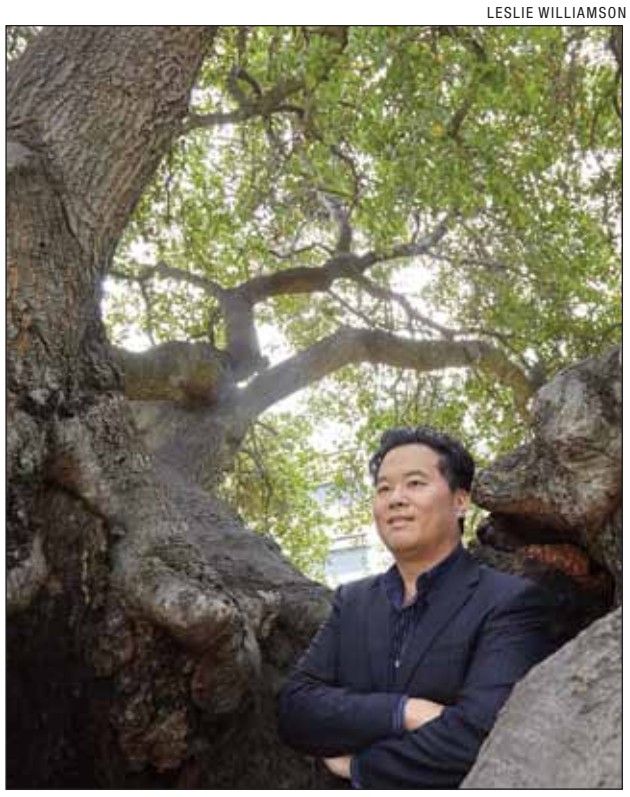
Precision: me includes podcasts in which he and Bailony discuss misconceptions about obesity — fat people are lazy, make bad choices, just need to take better care of themselves — as well as the judgment and guilt Chu has felt over the years. "I'm really glad we have the website and the blog to show people: This is my world," he said during the "Frustration" podcast. "I ate 800 calories a day for 10 days, and I didn't lose any weight."

Ultimately, Chu did shed 48 pounds over the 90-day experiment. By Day 60, his hemoglobin A1C — a three-month average of blood sugar — had almost normalized, and his triglycerides, a type of fat in the blood associated with insulin resistance and heart disease, had plummeted. In one puzzling result, however, his low-density lipoprotein, or "bad cholesterol," increased. Perhaps sharing the data online, Bailony said, "will allow someone to pipe in and say, 'Hey, I know why.'"

Although the blog project is finished, the personalized approach is not. "As I come off the very-low-calorie diet, Dexy will be even more useful," Chu said. Based on how much his glucose spikes within an hour of eating, he is developing a "personal glycemic index" of foods.

"We don't know his long-term story," Bailony said. "Hopefully, he'll decide to share that." ISM

LESLIE WILLIAMSON



Larry Chu and his physician used Chu's health data to develop a personalized weight-loss plan. In 90 days, Chu lost 48 pounds and reversed prediabetes.

OF NOTE

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

CHARLOTTE JACOBS, MD, the Drs. Ben and A. Jess Shenson Professor of Medicine, Emerita, received the Hewlett Award in March. The award recognizes an exceptional physician with ties to Stanford and is named for Albert Walter Hewlett, professor and executive head of the Department of Medicine from 1916 to 1925. Jacobs is an oncologist whose work has had international impact on head and neck cancer treatment. She served as senior associate dean of the School of Medicine and helped establish the Stanford Cancer Center. She has also written several biographies, including *Jonas Salk: A Life*.

DIEGO JARAMILLO, MD, was appointed professor of radiology, effective Dec. 1. He was also appointed associate chair of the Department of Radiology and chief of radiology at the VA Palo Alto Health Care System. He specializes in pediatric radiology and is working to improve the strength and effectiveness of MRI.

KATRINA KARKAZIS, PhD, MPH, a senior research scholar with the Stanford Center for Biomedical Ethics, was awarded a Guggenheim Fellowship. A "midcareer" award, the fellowship recognizes exceptional capacity for scholarship and will provide her with funding for one year of work, beginning in 2017. Karkazis also received a collaborative research fellowship from the American Council of Learned Societies that will support her writing and research for a year beginning in 2016. Her work focuses on scientific and medical beliefs about gender, sexuality and the body.

KIRAN KHUSH, MD, was promoted to associate professor of medicine, effective Oct. 1. Her research focuses on the evaluation and selection of donors for heart transplantation and the diagnosis and treatment of post-transplant complications.

NICHOLAS LEEPER, MD, was promoted to associate professor of surgery and of medicine, effective Nov. 1. He is a vascular medicine specialist whose research focuses on the genetics of atherosclerosis.

MARLENE RABINOVITCH, MD, the Dwight and Vera Dunlevie Professor of Pediatric Cardiology, will give the J. Burns Amberson Lecture at the American Thoracic Society's annual meeting in San Francisco on May 15. The annual lectureship honors a scientist who has made major contributions to pulmonary research. Rabinovitch is being recognized for her research on pulmonary arterial hypertension.

FATIMA RODRIGUEZ, MD, a second-year cardiology fellow, has received an American College of Cardiology/Merck Research Fellowship in Cardiovascular Disease and Cardiometabolic Disorders. The one-year, $70,000 award will finance her research on inequities in cardiovascular care for Latinos.

OSCAR SALVATIERRA, MD, professor emeritus of surgery and of pediatrics, will receive the 2016 Pioneer Award from the American Society of Transplant Surgeons, the society's highest honor. The award recognizes significant contributions to the field of transplantation. The only other Stanford surgeon to receive the award was the late Norman Shumway, MD, PhD, who performed the first successful human heart transplant in the United States.

DAVID K. STEVENSON, MD, the Harold K. Faber Professor of Pediatrics and senior associate dean for maternal and child health, will receive the Joseph W. St. Geme Jr. Leadership Award from the Federation of Pediatric Organizations. The award, which will be given April 30 at the Pediatric Academic Societies' annual meeting in Baltimore, Maryland, honors a pediatrician who has made broad and sustained contributions to the field of child health. Stevenson's accomplishments include his research on neonatal jaundice, which has changed how the condition is managed around the world.

MEGAN TROXELL, MD, PhD, was appointed professor of pathology, effective Dec. 1. Her research focuses on breast pathology, renal pathology and immunohistochemistry. ISM

Charlotte Jacobs

Diego Jaramillo

Katrina Karkazis

Kiran Khush

Nicholas Leeper

Marlene Rabinovitch

Fatima Rodriguez

Oscar Salvatierra

David K. Stevenson

Megan Troxell

Neanderthal

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human and Neanderthal lineages at between 400,000 and 800,000 years ago. The last common ancestor of Neanderthals and humans — based on the Y chromosome DNA sequenced in the study — is about 550,000 years ago.

Scientists believe Neanderthals died out about 40,000 years ago.

Sequencing the Neanderthal Y chromosome may shed further light on the relationship between humans and Neanderthals. One challenge for the research team is to find out whether the Y chromosome Neanderthal gene variants identified were indeed incompatible with human genes.

The data for the study came from public gene sequencing databases. "We did not collect any data for this work," said Mendez. "It was all public data."

Another Stanford-affiliated co-author is former graduate student David Poznik, PhD.

A researcher at the Max Planck Institute for Evolutionary Anthropology also co-authored the study.

The work was supported by the Stanford Center for Computational, Evolutionary and Human Genomics; the National Science Foundation; the National Library of Medicine; and the Max Planck Society.

Stanford's departments of Genetics and of Biomedical Data Science supported the work. ISM