INSIDE STANFORD MEDICINE

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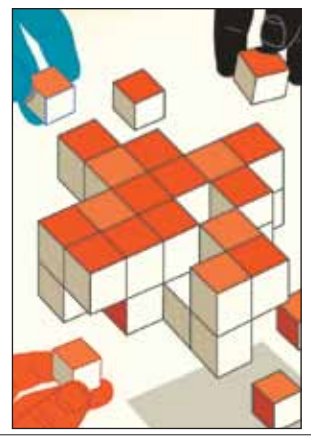

The new issue of *Stanford Medicine* reports on how researchers and clinicians are advancing precision health.

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Prenatal oxygen therapy helps baby with heart defect

By Erin Digitale

Linda Luna was five months pregnant with her first child when she got the bad news: Ultrasound scans showed a deadly defect in her baby boy's heart. He had a 90 percent chance of dying before or just after birth.

But thanks to groundbreaking treatment at Lucile Packard Children's Hospital Stanford, baby Liam, who went home to San Jose in January, is beating those odds. Now 3 months old, he is thought to be the first baby in the world successfully treated with prenatal maternal hyperoxygenation for his rare heart defect: congenital Ebstein's anomaly.

The problem at diagnosis? Because of severe leaks in two heart valves, blood flowed backward through the right half of Liam's heart. His heart became dangerously enlarged. Blood flow to the body was decreased by this backward See OXYGEN, page 6

ROBERT DICKS

Linda Luna holds her son, Liam, who was born at Lucile Packard Children's Hospital Stanford with a rare heart defect called congenital Ebstein's anomaly. He is believed to be first baby in the world successfully treated for the condition with prenatal maternal hyperoxygenation.

New blood test could transform diagnosis of active tuberculosis

By Jennie Dusheck

Researchers at the School of Medicine have identified a gene expression "signature" that distinguishes patients with active tuberculosis from those with either latent tuberculosis or other diseases.

The finding fills a need identified by the World Health Organization, which in 2014 challenged researchers to develop better diagnostic tests for active TB.

A paper describing the work was published online Feb. 19 in *Lancet Respiratory Medicine*.

WHO estimates that 9.6 million people got sick with TB in 2014 and that 1.5 million people died of the disease that year. Yet it remains difficult to diagnose.

"One-third of the world's population is currently infected with TB. Even if only 10 percent of them get active TB, that's still 3 percent of the world's population — 240 million people," said Purvesh Khatri, PhD, assistant professor of medicine and senior author of the paper.

Purvesh Khatri

Traditional diagnostic methods, such as the skin prick test and interferon assays, can't separate patients with active TB from those who are no longer sick or have merely been vaccinated against TB (and most countries vaccinate everyone against TB). These older diagnostics can miss cases of TB in patients with HIV.

A sensitive test

A common way to test for TB is to look for the disease-causing bacterium in sputum samples coughed up by patients. But sometimes it's hard for people to produce spu- See TB, page 7

Compound destroys malaria parasites, spares human cells

By Bruce Goldman

School of Medicine investigators have designed a compound that kills the parasitic microorganisms responsible for malaria but avoids harming human cells.

The compound exploits tiny structural differences between the parasitic and human versions of an intercellular protein-recycling machine called the proteasome.

Malaria, one of the world's most devastating infectious diseases, exacts a yearly toll of more than 400,000 deaths, mostly of children younger than 5. Mortality rates are dropping because of large-scale global intervention efforts, but malaria's prevalence remains stubbornly high, with hundreds of millions of people newly infected each year in sub-Saharan Africa and Southeast Asia.

Some 2.3 billion people — one-third of the Earth's people — are at risk for infection with the parasite.

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Bloods cells pillaged

Malaria is caused by protozoans of the genus Plasmodium. Five different species of Plasmodium are known to cause malaria in humans, with most deaths caused by one species, *P. falciparum*. Transmitted by mosquitos, the microbes invade the body, first holing up in the liver and then penetrating and replicating in red blood cells, which they ultimately destroy as they break out in search of new red blood cells See MALARIA, page 7

Worried about jet lag? Exposure to flashing light may prevent it

By Tracie White

Exposing people to short flashes of light while they're sleeping could provide a fast and efficient method of preventing jet lag, according to a study by researchers at the School of Medicine.

"This could be a new way of adjusting much more quickly to time changes than other methods in use today," said Jamie Zeitzer, PhD, assistant professor of psychiatry and behavioral sciences.

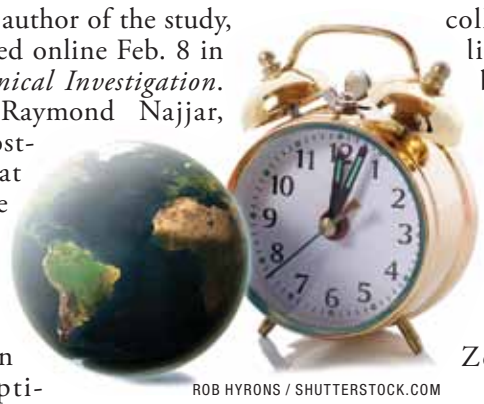
Zeitzer is senior author of the study, which was published online Feb. 8 in the *Journal of Clinical Investigation*. The lead author is Raymond Najjar, PhD, a former postdoctoral scholar at Stanford now at the Singapore Eye Research Institute.

Researchers led by Zeitzer have been working on developing an optimal technique for using light exposure to help people adjust more quickly to changes in their sleep cycles. Current light-therapy treatments for sleep disturbances include sitting in front of bright lights for hours at a time during the day, which allows you to transition your body clock to a new time zone in small steps prior to taking a trip.

Night light

In an earlier study, Zeitzer and his colleagues found that light therapy works best at night because the body's circadian rhythms, which control sleep cycles, are more sensitive to light at night, even through closed eyelids.

In the latest study, Zeitzer and Najjar



ROB HYRONS / SHUTTERSTOCK.COM

See JET LAG, page 6

Study: Marker signals most basic form of blood stem cell

By Christopher Vaughan

After a long series of experiments, researchers at the School of Medicine have identified a unique cell marker that they say allows them to pick out the most fundamental form of the stem cell that gives rise to the blood and immune system.

If confirmed, their finding would help settle long-standing controversies about the identity of these stem cells and their support cells. It also may pave the way for understanding how these cells maintain themselves, and provide scientists with the necessary information to grow blood stem cells in the laboratory or clinic.

NORBERT VON DER GROEBEN

Nearly 30 years after the discovery of hematopoietic stem cells, Irving Weissman and his colleagues have found a marker that allows them to study the version of these cells that continues to replicate.

A paper describing the research was published Feb 11 in *Nature*. Irving Weissman, MD, a professor of pathology and of developmental biology at Stanford, is the senior author.

In 1988, Weissman and his colleagues isolated the hematopoietic stem cell, which goes on to become the body's blood and immune cells. Since that time, researchers have had only mixed success in their attempts to get a detailed picture of how these HSCs maintain themselves and grow in the body. Over the years, it became clear why. The hematopoietic stem cells they isolated came in two flavors: most are short-term HSCs that lose their powers of replication over time, while a small fraction are long-term HSCs that can replicate indefinitely and are critical to lifelong blood production. To understand how other cells nurture the HSC, researchers needed to study only the long-term HSC.

With the new study, the Stanford researchers believe they have now found a reliable way to tell the difference between long-term and short-term HSCs. "In this paper we have found a single marker that, in the entire bone marrow, is only found in these long-term stem cells," said Weissman, who is also the Virginia and D.K. Ludwig Professor in Clinical Investigation in Cancer Research and the director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

Now that the researchers can identify the long-term HSCs, they hope to be able to look at how those cells and nearby cells create a "niche" — a biological space where long-term stem cells are supported and maintained.

"For nearly 30 years, people have been trying to grow HSCs outside the body and have not been able to do it — it's arguably the 'holy grail' in this field," said James Y. Chen, an MD/PhD candidate at Stanford and co-lead author of the paper. "Now that we have an anchor, a way to look at long-term HSCs, we can look at the cells around them to understand and, ideally, recreate the niche." If that niche can be created in a laboratory setting, people may be able to grow long-term HSCs in the lab.

A two-year search

In the last decades, many scientists have proposed various markers that they felt were unique to long-term HSCs, but the reliability of each proposed marker has been heatedly debated by other research groups, said postdoctoral scholar Masanori Miyanishi, MD, PhD, the other lead author.

To settle the issue, Chen and Miyanishi devised a method that was highly systematic, but also expensive and time-consuming. "Many times, we were about to quit," Chen said.

It's arguably the 'holy grail' in this field.

They started with a list of over 100 genes that are expressed in the bone marrow, where long-term HSCs are found, that seemed like good candidates to be unique markers of long-term HSCs. With the assistance of their colleagues, they eliminated genes that are turned on in areas of the bone that don't involve the creation of new blood and immune cells. That narrowed the field to 45 genes.

Then they performed a sophisticated, painstaking analysis to determine how much protein these genes were making in various cells. They found that only three proteins were produced at a high enough level to mark HSCs. Finally, they needed to find if one of these three was turned on in long-term HSCs and turned off in short-term HSCs. Although they couldn't yet identify which cells were long-term HSCs, they knew that any collection of HSCs should have both long-term and short-term HSCs, so they expected to find the candidate gene turned completely off in some cells and on in others. They found that only one gene fit that bill: a gene called Hoxb5.

The researchers point out that there may be other unique markers of long-term HSCs, such as genes that weren't among the initial group of the more than 100 they screened. But among the screened genes, only Hoxb5 was a unique identifier of the long-term stem cell.

Finding the niche

The researchers were also able to solve another key mystery by showing where in the bone marrow long-term HSCs reside. Satoshi Yamazaki, PhD, a member of the Tokyo lab of Stanford genetics professor Hiromitsu Nakauchi, MD, PhD, used technology recently developed in Japan to prepare bone marrow tissue and do computational analysis that validated the location and architecture of the HSC niche. "More than 90 percent of these cells reside on a particular type of blood vessel called venous sinusoids," said Nakauchi, a co-author of the paper.

The ability to identify long-term stem cells will give scientists a powerful tool for further study, the researchers said. "This opens the way to observe long-term HSCs and other cells in the niche as they exist in the body, without transplanting them," said Weissman, who is also director of the Ludwig Center for Cancer Stem Cell Research and Medicine. "This is how science works, by getting down to the purest irreducible element — in this case, blood stem cells — in order to develop new tools and understandings."

Other Stanford co-authors of the paper are instructor Rahul Sinha, PhD, and technicians Kevin Kao and Sean Wang.

The research was supported by the National Institutes of Health; the Virginia and D. K. Ludwig Fund for Cancer Research; the Siebel Stem Cell Institute; the Stanford University Medical Scientist Training Program; the National Heart, Lung and Blood Institute; the Human Frontier Science Program; the Uehara Memorial Foundation; the Toyobo Biotechnology Foundation; and the Kanzawa Medical Research Foundation.

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

New study finds that lower-back MRI scans are overused at VA

By Becky Bach

Between 30 and 50 percent of lumbar spine MRIs conducted through the Department of Veterans Affairs are inappropriate, according to a study by researchers at the School of Medicine and the VA.

The study, published online Feb. 2 in *The American Journal of Managed Care*, examined all lumbar spine MRIs prescribed in the entire VA system in fiscal year 2012.

"This imaging modality is widely used and, in many cases, used inappropriately," said Risha Gidwani, DrPH, lead author of the study and a health economist at the VA Health Economics Resource Center and an associate at Stanford Health Policy.

These MRI scans are used to diagnose the source of lower back pain, a condition that sidelines millions of Americans each year. But the best treatments for most cases of lower back pain are conservative. In many cases, they resolve on their own or with appropriate exercise within weeks, the study said.

In addition, radiographic findings on MRIs are often unrelated to patient symptoms, and MRIs can lead to unnecessary treatments that don't help patients feel better. Extra scans also rack up costs and lead to inefficient allocation of resources, Gidwani said.

The Centers for Medicaid and Medicare Services have developed guidelines that identify inappropriate lumbar spine MRIs. These guidelines specify what conditions warrant an immediate MRI. In all other cases, the guidelines recommend visits with a physician to evaluate and manage the condition and physical therapy or chiropractic care in the 28 to 60 days before ordering an MRI.

Several hypotheses have been suggested to explain the overuse of lumbar spine MRIs, Gidwani said. Fee-for-service physicians could be trying to add to their bottom line, or physicians could be practicing defensive medicine, seeking to avoid lawsuits, she said. To investigate this, she and her colleagues studied ordering decisions in the VA, where physicians are salaried and largely shielded from malpractice concerns.

Using the most permissive parameters — for which a visit to any physician for any reason preceding an MRI was considered management for lower back pain — the researchers found 31 percent of lumbar spine MRIs were inappropriate. Within the VA alone, those inappropriate scans cost $13.6 million. By limiting the definition of "appropriate" to only cases in which the physician appointment had a billing code for "lower back pain," the percentage of inappropriate scans skyrocketed to 53 percent. The real figure lies somewhere in the middle, Gidwani said.

"It's possible, and even probable, this percentage is even higher outside the VA," Gidwani said. "This study provides evidence this needs to be studied in different health-care environments where financial incentives may exacerbate the problem."

Paul Barnett, PhD, director of the VA Health Economics Resource Center and an associate at Stanford Health Policy, was the senior author.

Other Stanford-affiliated co-authors of the study are Steven Asch, MD, professor of medicine, and Patricia Sinnott, PhD, a health economist at the VA Health Economics Resource Center and an associate at Stanford Health Policy.

This work was supported by a grant from the VA. ISM

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STANFORD MEDICINE

Previously unknown bacterial species found in dolphins

By Steve Fyffe

U.S. NAVY

U.S. NAVY

Researchers studying U.S. Navy dolphins, such as the one shown at top, found that about three-quarters of the bacteria in the mammals' mouths had never before been identfied. The Navy's trained sea lions, such as the one above, were found to share many types of bacteria with terrestrial carnivores.

School of Medicine researchers working with the U.S. Navy's Marine Mammal Program in San Diego have discovered a startling variety of newly-recognized bacteria living inside the trained dolphins that the Navy uses to find submerged sea mines and detect underwater intruders. They found similar types of bacteria in wild dolphins as well.

"About three-quarters of the bacterial species we found in the dolphins' mouths are completely new to us," said David Relman, MD, professor of medicine and of microbiology and immunology. These previously unknown bacteria represent "whole new realms of life," according to Relman, who is also co-director of the Center for International Security and Cooperation at Stanford and a senior fellow at the university's Freeman Spogli Institute for International Studies.

A paper describing the research was published Feb. 3 in Nature Communications. Relman is the senior author. The lead author is Elisabeth Bik, PhD, a research associate in his lab.

"Bacteria are among the most well-studied microbes, so it was surprising to discover the degree to which the kinds of bacteria we found were types that have never been described," Relman said. "Novelty doesn't just mean new names of species, families, classes or phyla. … There's reason to believe that, along with this taxonomic novelty, there's functional novelty."

Dolphin breath

The U.S. Navy has been training dolphins and sea lions to carry out defensive military missions from their bases in San Diego and elsewhere since the early 1960s.

Relman, who is also the Thomas C. and Joan M. Merigan Professor, started working with the Navy more than 15 years ago to identify bacteria suspected of causing stomach ulcers in their dolphins.

His latest project to catalog the bacterial communities, or microbiota, living inside the dolphins began when the Navy asked him to help develop a probiotic bacterial strain that could keep their dolphins healthy, or help sick dolphins get better.

Navy trainers took regular swabs from the dolphins' mouths and rectal areas and shipped the samples to Stanford on dry ice for analysis.

They also collected samples of the respiratory fluids and other biological matter in the air that the dolphins exhaled from their blowholes onto sterile filter paper, as well as samples of their gastric juices using a tube that the dolphins would swallow on command, and, for comparison, bacteria from the surrounding water.

The study found a similar amount of diversity and novelty in bacterial samples taken from wild dolphins living in Sarasota Bay, off the west coast of Florida, although there were slight differences in the bacteria from the dolphins' mouths.

Hoping to develop diagnostic tests

Relman said he hoped to develop a profile of the normal microbial communities in healthy dolphins and other marine mammals so that scientists could detect any early change that might signify an imminent disease, or health problems caused by climate change and ocean warming.

"There's a lot of concern about the changing conditions of the oceans and what the impact could be on the health of wild marine mammals," Relman said. "We would love to be able to develop a diagnostic test that would tell us when marine mammals are beginning to suffer from the ill effects of a change in their environment."

The research could help solve other mysteries, such as how dolphins digest their food, even though they swallow fish whole without chewing them. The answer might lie in a unique bacterial group that's also been identified in an endangered species of freshwater dolphins living in China's Yangtze River, Bik said.

"It's a very intriguing bacterial group that nobody has seen before in any terrestrial animal group," said Bik. "I would really love to know more about those bacteria and sequence their genomes to understand more about their functional capacity."

NATIONAL MARINE MAMMAL FOUNDATION

A swab is taken from a dolphin's mouth to study the bacteria living there.

Microbiota differences in sea lions, dolphins

The study also examined oral, gastric and rectal samples from the Navy's trained sea lions. "The sea lions and dolphins are kept at the same facility, they're fed exactly the same fish, and they're swimming in the same water … but they're very, very different in terms of microbiota," Bik said.

Unlike dolphins, sea lions share many common types of bacteria with their terrestrial cousins.

"Sea lions weren't that different from other carnivores like dogs and cats," Bik said. "They're evolutionarily related to them, and their microbiota looks very similar to those animals. But dolphins don't really have a terrestrial mammal that's closely related, and their microbiota looks very different from anything else that people have seen."

Relman said his team was planning on expanding their study to include other marine mammals such as sea otters, killer whales, grey whales, harbor seals, elephant seals and manatees. Their purpose, in part, is to understand how life in the sea, over the millions of years since mammals returned to it, may have shaped the structure of their microbial communities and the roles they play in marine mammal health.

Orca stool

They're already analyzing more than 80 samples of killer whale stool that the U.S. National Oceanic and Atmospheric Administration has gathered with the help of specially trained sniffer dogs, which stand on the bow of their boats and point to fresh orca feces before it sinks.

The California Department of Fish and Wildlife is contributing oral and rectal swabs from the sea otters and seals it studies as part of its conservation, ecological and monitoring programs.

And the Marine Mammal Center in Sausalito, which is the West Coast's largest rescue and rehabilitation facility for marine mammals, is sending oral and rectal swab samples from the seals in its care.

Relman said the research could help scientists begin to answer fundamental questions about life in the ocean.

"Marine mammals remain one of the more poorly understood habitats for studying microbial life, and there would be lots of reasons for thinking that these are important habitats to study, in part because of the relevance for the health of these marine mammals, but also because they represent a view into what it means to live in the sea and the nature of our relationship with this aspect of our environment," Relman said.

Other Stanford-affiliated co-authors of the paper are research associate Elizabeth Costello, PhD; graduate student Alexandra Switzer, DVM, MPVM; postdoctoral scholar Benjamin Callahan, PhD; and Susan Holmes, PhD, professor of statistics.

Researchers from the National Marine Mammal Foundation, the Sarasota Dolphin Research Program and the Space and Naval Warfare Systems Center Pacific also contributed to the study.

The research was supported by Office of Naval Research, the National Institutes of Health, the National Science Foundation and the Thomas C. and Joan M. Merigan Endowment at Stanford.

Stanford's departments of Medicine and of Microbiology and Immunology also supported the work. ISM

Steve Fyffe is the communications manager at the Stanford Center for International Security & Cooperation.

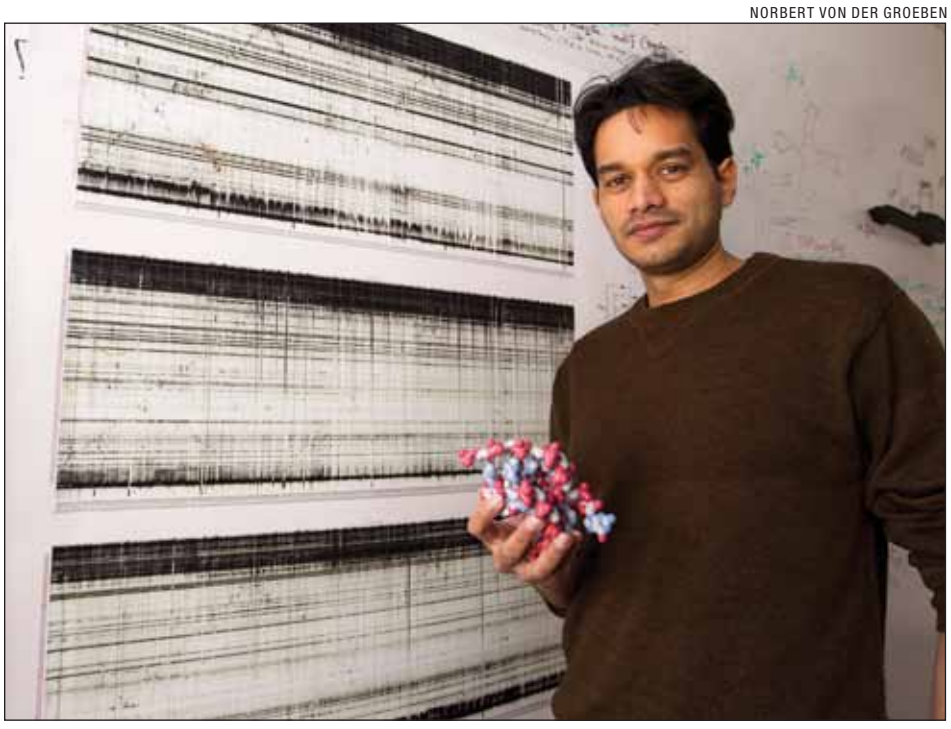
Video-gamers publish findings on designing RNA structures

By Bruce Goldman

A scientific paper written by video-gamers has been accepted for publication in a peer-reviewed journal, perhaps the first time since the days of Benjamin Franklin that work led by non-credentialed "citizen scientists" will appear in such a format.

The paper describes a new set of rules, derived intuitively by players of a video game called Eterna, for determining the difficulty of designing desired structures composed of RNA molecules. Unlike previous crowdsourcing efforts for which scientific experts have reached out to online gamers, the gamers themselves took the lead in this paper. Three experienced Eterna gamers distilled their community's ideas into online Google documents and then contacted expert researchers at the School of Medicine and elsewhere to independently test their ideas using high-performance supercomputers. The final paper, published online Feb. 16 in the *Journal of Molecular Biology*, is a condensed version of the gamers' own documents.

NORBERT VON DER GROEBEN



VINEET KOSARAJU

Rhiju Das, top, helped create a video game that allows players to design chemical sequences of RNA that fold stably into desired shapes. A screen shot of a virtual RNA molecule from the game.

Once dismissed as a relatively boring component of living cells, RNA is now understood to underlie virtually every critical process in biology and is increasingly appreciated as a potential medical and industrial tool. While each RNA molecule begins its existence as a linear chain of subunits, it quickly folds into a thermodynamically stable shape that depends on the molecule's particular sequence of component subunits. That shape, in turn, dictates which cell components the RNA molecule will interact with and how. Scientists' improving ability to computationally model and design RNA raises the promise of a new generation of RNA-based therapies customized to specific cancers, viruses, neurological abnormalities and inherited disorders.

Crowdsourcing scientific discovery

The paper, which will also appear in March in a special print issue of the journal devoted to RNA design, signifies an evolution of how crowdsourcing can impact scientific discovery, said its senior author, Rhiju Das, PhD, associate professor of biochemistry at Stanford. The paper's research was not guided or collated by expert scientists, as has been the case in prior work from Eterna and other scientific discovery projects, but by the non-experts in the gaming community. "It's important to capture these insights and make them both public and credible via publication in peer-reviewed journals," he said.

To play the game, no special skills or biochemistry training are required.

One striking finding of the Eterna consortium (known as the Eterna Massive Open Laboratory): RNA molecules that are symmetrical, pleasing to the eye and that fold stably are also hard to design; the more symmetrical the desired shape, the more difficult to achieve it.

Launched in 2011 by Das and Adrien Treuille, PhD, an assistant professor of computer science at Carnegie-Mellon University, Eterna now boasts more than 100,000 registered players, said Das. The interactive online video game challenges players to design chemical sequences of RNA that fold stably into desired shapes. Sequences that look promising in terms of their thermodynamic stability — as predicted by algorithms whose job it is to assess this feature — are synthesized in Das' laboratory and tested to see what structure the RNA sequences actually assume.

Anyone age 13 or older can register to play by going to the game's official website, Eternagame.org. No special skills or biochemistry training of any sort are required.

"It's not even necessary to know what RNA is or does," Das said.

Rating RNA-design difficulty

Until now, there has been no established rating scale for RNA-design difficulty, Das said. A biomedical researcher is not able to easily assess the difficulty of designing an RNA structure for a diagnostic or therapy, and therefore may waste significant time and money trying to create difficult or near-impossible shapes for an RNA molecule to assume. Even though attaining a rating scale for RNA design was not the mission of Eterna, experienced Eterna gamers noted how useful such a difficulty rating would be in guiding new players from easier to harder "puzzles." These experienced gamers took it upon themselves to compile a list of particular features that render RNA shapes difficult to design sequences for. They carried out tests using their own personal

See ETERNA, page 5

Stanford Medicine issue reports on precision health

By Rosanne Spector

New tools and technology are leading medical experts at Stanford Medicine to think big. Really big.

"For as long as people have been caring for the sick, we have been playing a frantic game of catch-up, working to cure illness after the fact," said Lloyd Minor, MD, dean of the Stanford School of Medicine, in the new issue of *Stanford Medicine* magazine.

"Now, for the first time in our history, we are starting to see the possibility to not just win the race against the clock, but to win it before it even begins — to prevent disease before it strikes and cure it decisively if it does. This is the power of precision health."

In the special report in *Stanford Medicine* magazine's winter issue, you'll read how Stanford researchers and clinicians are working toward this goal.

"Our vision," said Minor, "is that a doctor can tailor every therapy specifically to what's known about a patient: their genetics, their metabolomics, all their -omics, their imaging, everything about them. At Stanford, we want to live in a world where health-care providers aren't left on their own to somehow aggregate all that information. Instead, information technology helps a doctor to confidently tell the patient, 'You are going to benefit most from doing the following.' We know it will take a sea change in training the doctors of the future, but the benefits will be massive."

The magazine also includes an excerpt from the best-selling memoir *When Breath Becomes Air*, by Paul Kalanithi, MD, in which the author reflects on life in light of his impending demise. At 35, the Stanford neurosurgeon faced terminal cancer.

Special report highlights

Highlights of the special report include:

- An article describing the aims of precision health and the tools being used to carry it out.
- A feature on how insights from neuroscience could customize care for people with anxiety, depression and other psychiatric conditions.
- A Q&A with news icon Tom Brokaw about dealing with cancer and what it taught him about the U.S. health-care system. The online version includes audio of the complete conversation.
- A story about a family coping with the risk of premature birth and about research uncovering how to predict and prevent it.
- An article describing ways nanotechnology is being used to see, monitor and destroy cancer cells.
- A feature about revolutionizing the practice of medicine by drawing on massive pools of data hidden in electronic medical records to individualize treatments.
- A piece on Stanford's Letter Project, which helps you specify to doctors and family how you'd like to live your last days.
- An additional feature explains how new laboratory techniques for growing drugs originally derived from plants could reduce shortages and lead to more effective compounds.

The magazine is available online. Print copies are being sent to subscribers. Others can request a copy at (650) 723-6911 or by sending an email to medmag@stanford.edu. **ISM**

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Frank Longo on the fight against Alzheimer's

Frank Longo, MD, PhD, is professor and chair of neurology and neurological sciences and co-leader of the new Stanford Neuroscience Health Center, which opened in January. Within the center's five floors are physician experts and care teams in 21 neuroscience subspecialties. All these clinicians come together in the new center to provide coordinated leading-edge treatments for complex neurological conditions.

Longo, the George E. and Lucy Becker Professor in Medicine, runs a research lab that has secured funding from the Alzheimer's Association, the Alzheimer's Drug Discovery Foundation, the National Institutes of Health and others. He and his team, along with collaborator Stephen Massa, MD, PhD, at UCSF and the San Francisco VA Medical Center, pioneered the development of novel small molecules that counteract the degenerative signaling mechanisms that occur in Alzheimer's and other neurodegenerative disorders. One of these compounds is currently in clinical testing.

Longo recently spoke with writer Sara Wykes about Alzheimer's disease, recent research breakthroughs and the new center, including its key features and services available to Alzheimer's patients.

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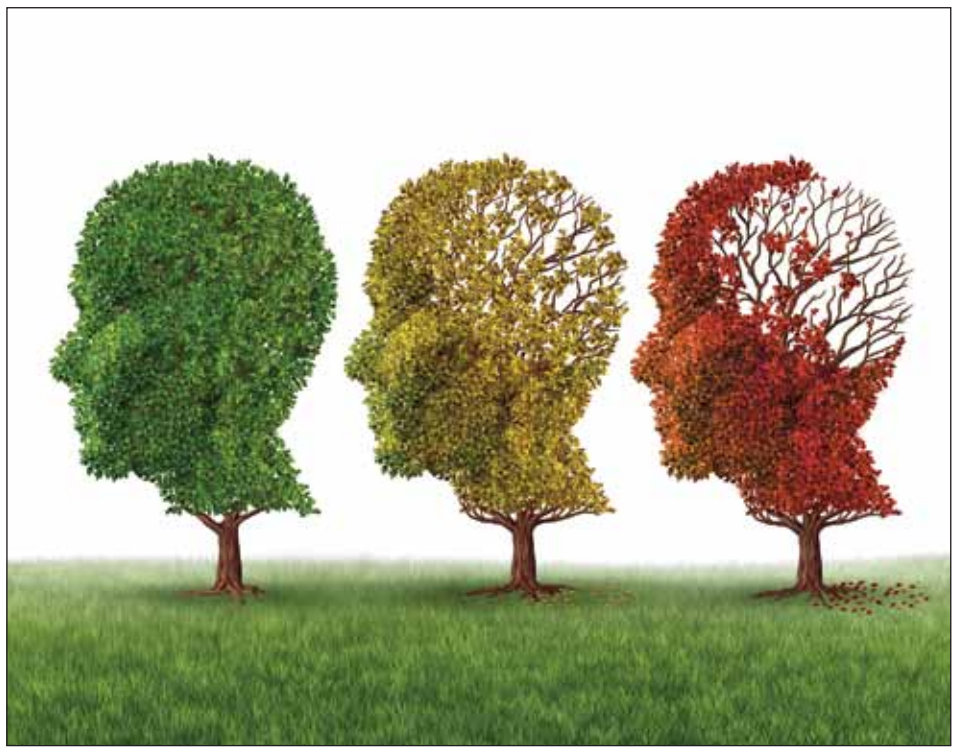


1 How does Alzheimer's disease affect the brain?

LONGO: Alzheimer's affects the networks in the brain that are the cornerstone of our ability to learn and remember. Those networks are dynamic: If the connections, or synapses, aren't used, they disappear. With Alzheimer's disease, two proteins in the brain interfere with those synaptic connections: The amyloid protein breaks into fragments that are toxic to the connections, and the tau changes into abnormal folds and clusters that are also toxic to the connections. As we lose those connections, we lose our memories, our ability to recall them and our ability to form new ones. The accumulation of those two toxic forms of proteins, in conjunction with inflammation in the brain produced by other causes, including aging, is what breaks down the synapses.

We don't yet know the exact cause for Alzheimer's or for the accumulation of these toxic proteins. We do know that these processes are influenced by genetics. People with a parent who has Alzheimer's are at a two-fold risk of developing Alzheimer's.

People with early-onset Alzheimer's — generally defined as dementia that appears before age 60 — have a 50 percent chance of passing the gene causing the disorder on to each of their children.

2 How can I tell the difference between normal memory lapses and Alzheimer's?

Frank Longo

LONGO: Our ability to recall memories naturally slows with age. Our intelligence remains the same, but we may need more time to recall certain things from our memory.

The next stage of memory change is called mild cognitive impairment. People other than the person who has MCI may notice a slowing of memory. The loss is not usually substantial enough to interfere with someone's daily life.

For some, however, MCI progresses to dementia. Dementia is diagnosed when someone has a loss of function in two or more areas of cognition — such as memory, verbal ability, visuospatial function or judgment — severe enough to significantly affect day-to-day function. There are many potential causes of dementia, but Alzheimer's is by far the most common.

3 What research is happening here on Alzheimer's disease?

LONGO: We are very excited here at Stanford Medicine about our recent selection as one of a few National Institutes of Health-funded Alzheimer's Disease Research Centers, or ADRCs, in the country. The NIH designation comes with a $7.3 million funding award over a five-year period to advance our research.

Associate professor of neurology Michael Greicius, MD, medical director at the Stanford Center for Memory Disorders and the director of the imaging section at the Stanford ADRC, has recently had great success in developing new imaging methods to examine Alzheimer's patients. He uses functional MRI and PET scans to track, for the first time, the function of synapses and the accumulation of those extra proteins that interfere with memory function in Alzheimer's patients.

He is also discovering genes that appear to protect the brain from accumulations of toxic amyloid and tau. He has identified people well into their 90s whose PET scans show they have normal cognitive function despite having large amounts of amyloid in their brains or the high-risk ApoE4 gene generally associated with earlier onset of dementia.

One of the most powerful substances known to promote the maintenance of synaptic connections is a protein called brain-derived neurotrophic factor. BDNF, like most proteins, would not cross the brain's protective barrier if it were simply administered as a drug. In its natural protein form, BDNF also would be likely to have side effects. My research team pioneered the development of small molecules that mimic key features of BDNF. These small molecules can get across the brain barrier and prevent degeneration of synapses and other Alzheimer's-related events. Studies in mice with Alzheimer's are going well.

Most recently, a research team led by professor of neurology Tony Wyss-Coray, PhD, built upon the work of professor of neurology Thomas Rando, MD, PhD, an expert in the biology of aging, by showing that the cognitive abilities of old mice could be improved with an infusion of blood from young mice. Wyss-Coray and his team discovered that the most crucial element of the blood linked to that improvement was a protein in plasma called colony-stimulating factor 2. That's another very exciting discovery because CSF2 is already FDA-approved for people who have received bone marrow transplants. From many decades of use, we also know plasma is safe.

Inspired by these mouse studies, clinical assistant professor of neurology Sharon Sha, MD, is running a trial in which blood plasma, obtained from the Stanford Blood Center from young, healthy volunteers, is being administered to Alzheimer's patients to determine if that plasma can improve cognition.

We are also looking at new ways to combine some of the medications and treatments we already have to slow the disease process. We know from the example of HIV that although the effects of one drug might be small, a combination of drugs can be highly effective.

4 Some companies tout brain games or nutritional supplements as protective against Alzheimer's. Do they work? What is the best prevention strategy?

LONGO: In October 2014, the Stanford Center on Longevity and the Max Planck Institute for Human Development released a statement, signed by nearly 70 researchers, to share our concern that the claims made for these types of games are not supported by substantial scientific evidence. The question is not if you can improve your ability to play a certain computer game but whether that improvement will appear in other tasks you might do. There is no reliable evidence to support such a spillover.

There are also no current reliable and sufficiently sized studies that show a direct link between an increase in cognition and adding coconut water or oil, omega-3 fatty acids, DHA, vitamin D or turmeric to your diet.

The most important and research-validated approach to reduce your risk is exercise. Research has shown that 30 minutes a day, five days a week, preferably at a moderate level, reduces the risk for Alzheimer's.

Risk for Alzheimer's can also be influenced by diet, high blood pressure and diabetes. We recommend a Mediterranean diet as a part of an overall plan to reduce your risk of Alzheimer's, high blood pressure and diabetes.

We have also recently learned that disrupted sleep does not allow the brain to clear amyloids. That knowledge leads us to believe that long-term sleep disruption and the interference with amyloid clearing could also raise your risk of Alzheimer's.

We can't prevent the influence of aging on the risk of Alzheimer's. The likelihood of Alzheimer's increases with age, in part because toxic forms of amyloid protein, tau protein and inflammation in the brain all increase with age. By age 85, four out of 10 people will have been diagnosed with the disease. Nor can we change our genetic risk: About 2 percent of Alzheimer's appears in people at a young age — in their 40s or 50s — because of their genetics.

5 What are the treatment options for Alzheimer's disease and other dementias?

LONGO: Unfortunately, there are no currently available FDA-approved medications proven to delay onset or slow progression of the underlying brain degeneration and loss of synaptic connections that occur in Alzheimer's disease. There are, however, two groups of FDA-approved medications that can temporarily boost the chemical neurotransmitters at synapses and so produce a modest improvement in cognitive function. We offer clinical-trial use of these medications. They do have side effects.

Along with these medications, we strongly encourage physical exercise, a healthy diet and weight, and continued cognitive engagement that could include socializing, hobbies or any other activities that encourage brain function. We work closely with our patients' primary care physicians to make sure their patients have optimal levels of B12, vitamin D, thyroid hormone and other substances. We also keep an eye out for any trials, regardless of location, which might benefit our patients. **ISM**

Eterna

continued from page 4

computers. They then contacted scientists in Das' lab with a set of predictions to test their ideas — a set of 100 hypothetical RNA shapes that experienced Eterna players rated from relatively "designable" to nearly "intractable." The scientists used Stanford supercomputers to test these predictions against a half-dozen standard algorithms developed for the purpose of supplying RNA sequences that fold into specified shapes, and they found that the players' rankings correlated strongly with the algorithms' ability to solve these puzzles. Indeed, the hardest puzzles, which could be solved by experienced Eterna players, were not solvable by any of the algorithms even when given numerous days of computer time.

In some cases, these now-confirmed intuitions overthrow conventional thinking in the RNA-design community about which designs are likely to be attainable and which intractable, Das said. For instance, "the players discovered on their own, and the algorithms independently confirmed, that the more symmetrical a requested structure is, the harder it will be to design," he said.

Lead authors of the paper are Eterna gamers Jeff Anderson-Lee, Eli Fisker, Vineet Kosaraju and Michelle Wu, of the Eterna Massive Open Laboratory. Wu is also a PhD student in biomedical informatics at Stanford.

Funding for the study was supplied by the W.M. Keck Medical Research Foundation, the Burroughs-Wellcome Foundation, the National Institutes of Health and the National Science Foundation.

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

Oxygen

continued from page 1

flow, causing fetal heart failure. Left untreated, the defect would result in death either before or shortly after birth.

Devising a new approach

"Once you see the type of leakage Liam had, it's usually a progressive process," said Theresa Tacy, MD, associate professor of pediatrics at the School of Medicine and Liam's fetal cardiology specialist. "It just gets worse: The fetus eventually develops heart failure and dies."

To improve Liam's prognosis, Tacy wanted to change his blood flow before birth. In two prior cases of Ebstein's anomaly, she had administered anti-inflammatory medications to the pregnant mothers. These drugs constricted a specific blood vessel, helping to normalize blood flow to the body. Although this approach helped both babies to survive until birth, a combination of high blood pressure in the lungs and the severe Ebstein's anomaly caused both to die soon after. The trouble was that when the babies were born, little to no blood could be pumped from the heart to the lungs.

So this time, Tacy worked with a team of more than 30 experts from a variety of disciplines at the hospital's Fetal and Pregnancy Health Services to devise a new approach: Expectant mom Luna received 12 hours per day of high-flow oxygen through a face mask, starting when she was 33 weeks pregnant. The idea was to relax Liam's lung blood vessels with the extra oxygen he'd get from his mom. This would make it easier for his heart to pump blood forward into his lungs and, the doctors hoped, help him survive birth and the first few days of life, until he was strong enough to have his heart surgically repaired.

More bad news

At the same time they were devising Liam's treatment plan, the team observed a worrying decline in Luna's liver function. Her symptoms could signal a dangerous pregnancy complication known as mirror syndrome.

"We couldn't tell if mom was sick because of the baby's heart problem, which would indicate mirror syndrome, or if she had liver dysfunction for other reasons," said Luna's high-risk obstetrician, Katherine Bianco, MD, associate professor of obstetrics and gynecology. Mirror syndrome can lead to an obstetric emergency that requires immediate delivery of the baby, Bianco added. Because of the risky symptoms, Luna stayed in the hospital's antepartum unit for round-the-clock monitoring.

"Linda was always very positive and willing to do whatever it took, even though we told her so many times 'We don't think this baby is going to make it,'" Bianco said.

"We were trying to offer Liam's parents hope but also remain realistic," said David Axelrod, MD, assistant professor of pediatric cardiology. "We knew that even if he made it through pregnancy, his risk of dying during his first few days of life was very high."

On the morning of Nov. 22, about a month before her due date, Luna woke up having contractions. Liam's heart rate was unstable, and the physicians decided he should be delivered by C-section. He had received about three weeks of the prenatal oxygen therapy.

"I was very scared," Luna said. "But the medical team said 'We've been ready, we've been watching him closely, and you're ready to have him.'"

Oxygenating the blood

Liam was born that day at 5:47 p.m. The doctors immediately put him on an extracorporeal membrane oxygenation machine, a form of heart-lung bypass, to deliver oxygen to his blood. Katsuhide Maeda, MD, clinical assistant professor of cardiothoracic surgery, also surgically closed a blood vessel near the baby's heart to help his blood to flow forward. The team was in such a hurry that Liam wasn't even weighed at birth; saving his life took precedence. Once Liam was stable, Luna's husband, Jose Silva, returned to the recovery room to reassure her that their newborn had cleared an important hurdle.

"Jose told me that Liam's heart was doing it on its own, but he needed help breathing," Luna said. Around midnight, she visited Liam for the first time in the cardiovascular intensive care unit. "I didn't see him until he had his chest open and was on ECMO," she said. "It was very hard, the first time seeing my son, to see him like that."

"After he was born, Liam was severely ill," Axelrod said. Keeping newborns on ECMO is dangerous because they require blood thinners that put them at risk of bleeding and stroke. And the ECMO machinery can expose them to air bubbles and tiny blood clots that would further increase stroke risk. Yet without ECMO, Liam's body wouldn't get enough oxygen. Balancing the risks was "like trying to catch a falling dagger," Axelrod said.

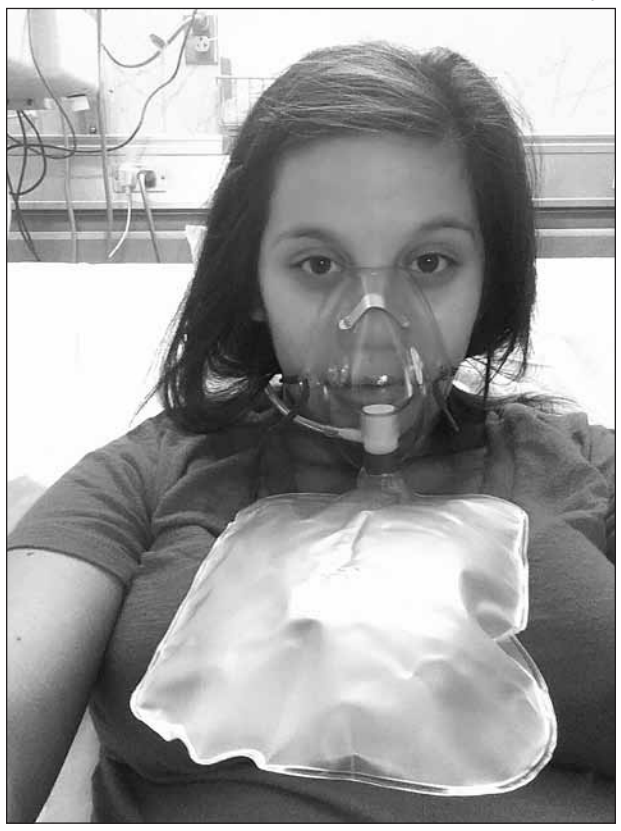
Finally, by Dec. 3, Liam's lungs were working well enough that the physicians thought he could probably get enough blood flow to them on his own, without the need for ECMO. In surgery that day, Frank Hanley, MD, professor of cardiothoracic surgery, fully repaired his heart, fixing the malfunctioning valves and reducing the size of the enlarged right atrium. After the surgery, Liam was removed from ECMO.

"It was a huge surgery for a tiny baby fighting for his life," said Luna. "The seven-hour wait during surgery was the longest wait of my life, but when they finally wheeled him out, he was a different baby. We were so thankful."

Liam is now doing well. He will be monitored as he grows by Axelrod, who is also his outpatient cardiologist, but the physicians expect he will otherwise be an ordinary kid. "He's got a great outlook, which is a really satisfying outcome," Axelrod said. "Our team did a great job."

Added Tacy, "This is just one case, but it's so exciting to move forward and feel a glimmer of what we think is the right path for treating other babies with this devastating heart defect." **ISM**

LINDA LUNA



Expectant mom Linda Luna received 12 hours per day of high-flow oxygen through a face mask, starting when she was 33 weeks pregnant.

Jet lag

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found that short flashes of light at night are more effective than continuous light exposure and could further speed up the process of adjusting to a different time zone before a trip.

The transfer of light through the eyes to the brain does more than provide sight; it also changes the biological clock. A person's brain can be tricked into adjusting more quickly to disturbances in sleep cycles by increasing how long he or she is exposed to light prior to traveling to a new time zone.

After arriving in a new time zone, the body will eventually adjust on its own, but at a slow pace of about one hour a day. Meanwhile, jet lag, which occurs because your body's clock is still synced to your original time zone, can cause fatigue, lack of alertness, a general feeling of malaise and sometimes gastrointestinal problems.

Biological 'hacking'

Light therapy is designed to speed up the brain's adjustment to time changes. By conducting light therapy at night, the brain's biological clock gets tricked into adjusting to an awake cycle even when asleep. It's a kind of "biological hacking" that fools the brain into thinking the day is longer while you get to sleep, Zeitzer said.

NORBERT VON DER GROEBEN

Jamie Zeitzer sets up a flashing light in his lab. His research shows that exposure to short flashes of light during sleep can help prevent jet lag.

To determine whether continuous or flashing lights would provide the fastest method of adjusting sleep cycles, researchers recruited 39 participants ranging in age from 19 to 36 and had them get on a routine sleep-wake cycle, going to bed and waking up at the same time every day for about two weeks. They then had the volunteers sleep in the lab, where some were exposed to continuous light for an hour and others were exposed to a sequence of flashes of various frequencies for an hour.

The study found that a sequence of 2-millisecond flashes of light, similar to a camera flash, 10 seconds apart elicited a nearly two-hour delay in the onset of sleepiness, the most efficient and fastest method of adjusting the internal clock. For participants exposed to continuous light, the delay was only 36 minutes.

Why it works

Two bits of physiology explain why flashing lights work better than a continuous light, Zeitzer said.

"The first is that the cells in the retina that transmit the light information to the circadian system continue to fire for several minutes after the stimulus — in this case, flashing light — is no longer there," he said. "The second is that the gaps of darkness between the light flashes allow the pigments in the eye that respond to the light to regenerate — that is, go from an inactive form that cannot respond to light to an active form that is able to respond to light."

Zeitzer explained how flashing-light therapy during the night could be used to adapt to traveling from California to the East Coast.

"If you are flying to New York tomorrow, tonight you use the light therapy. If you normally wake up at 8 a.m., you set the flashing light to go off at 5 a.m. When you get to New York, your biological system is already in the process of shifting to East Coast time."

He added, "We have found that most people can sleep through the flashing light just fine," and that flashing-light therapy used at night could be a great method of helping to adjust the internal biological clock for all kinds of sleep cycle disruptions — from medical residents whose sleeping schedules are constantly changing, to night-shift workers who want to be awake during daylight hours on the weekends, to sleepy truck drivers whose sleep schedules are constantly changing.

The research was supported by grants from the National Heart, Lung and Blood Institute and the Department of Veterans Affairs Sierra Pacific Mental Illness Research, Education and Clinical Center.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. **ISM**

Malaria

continued from page 1

to pillage.

"This penetration/replication/breakout cycle is rapid — every 48 hours — providing the opportunity for large numbers of mutations that can produce drug resistance," said Matthew Bogyo, PhD, professor of pathology. Consequently, several generations of antimalarial drugs have long since been rendered useless, he said.

Resistance to current front-line antimalarial drugs, known as artemisinins, is spreading and has been observed in a half-dozen Southeast Asian countries. But in a study published Feb. 11 in *Nature*, Bogyo and his colleagues showed, using laboratory-adapted clinical samples from Southeast Asia, that the new compound can effectively kill artemisinin-resistant malaria parasites and that low doses of the drug can further sensitize them to killing by artemisinin.

Bogyo shares senior authorship of the study with Paula da Fonseca, PhD, of the MRC Laboratory of Molecular Biology in Cambridge, UK. The lead author is Stanford graduate student Hao Li.

Protein chewers

Proteins, which perform the vast majority of the work done inside a cell, are assembled from building blocks called amino acids, which are linked together in a linear sequence like beads in a necklace.

The proteasome, a barrel-shaped cluster of proteins, chews up other proteins by breaking those amino-acid links. Proteasomes abound in all human cells and in all protozoans. They are crucial to the elimination of faulty proteins and to cell replication. So blocking their function wreaks havoc within a cell.

But compounds previously found to block proteasome activity in *P. falciparum* have tended to inhibit the human version of the proteasome, too, resulting in toxicity that would be unacceptable in a malaria drug.

In the new study, the Stanford team produced highly purified preparations of both human and *P. falciparum* proteasomes and then "fed" those two preparations a set of protein fragments collectively containing a vast variety of amino-acid linkages "in order to see which amino-acid linkages these proteasomes like to chew up," Bogyo said.

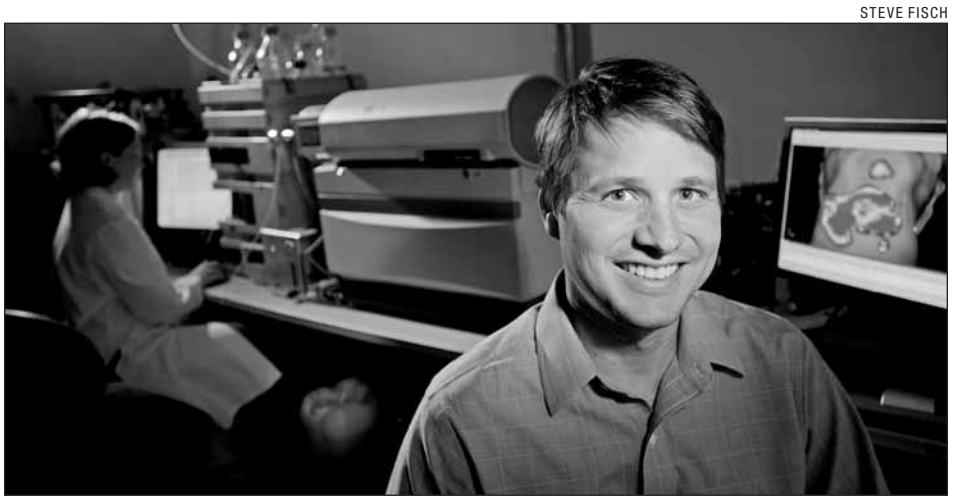
Clogging up the works

The team identified 117 amino-acid linkages that are readily chewed up by *P. falciparum* proteasomes but not so well by human proteasomes, and 153 where the reverse is the case. They used this information to design tiny protein snippets that failed to interact with human proteasomes but that, instead of getting chopped up by *P. falciparum* proteasomes, would gum up parts of them responsible for cleaving certain amino-acid links.

"They just stick and don't get released," Bogyo said. The clogged catalytic sites are now unable to break apart the linkages they were designated to cleave.

Next, the UK group investigated the basis for this selectivity by using a high-resolution version of electron microscopy to map the detailed structure of the parasite and human proteasomes. This allowed Bogyo's team to optimize the protein snippets they were using as parasite-selective proteasome inhibitors. The three-amino-acid snippet they ultimately focused on, called WLL, was able to gum up two different catalytic regions in *P. falciparum* proteasomes without any effect on those of cultured human cells. There was a 600-fold difference in WLL's potency at killing the parasitic cells over the human cells.

STEVE FISCH



Matthew Bogyo and his colleagues designed a compound that can kill malaria parasites without harming human cells.

Reducing parasites in mice

In experiments with mice with a murine version of malaria-inducing Plasmodium, the researchers saw a nearly complete reduction of parasites with both single and multiple doses of WLL. Still other tests, performed on artemisinin-resistant parasites infecting human red blood cells in laboratory cultures, suggested that the WLL compound was equally effective at killing artemisinin-resistant parasites and artemisinin-sensitive parasites.

Bogyo pointed out that the artemisinin family of drugs work by modifying proteins in the parasite. Resistance occurs when the parasites' proteasomes are able to recycle those modified proteins. But this means that artemisinin-treated parasites are particularly sensitive to disruption of normal protein function.

"The compounds we've derived can kill artemisinin-resistant parasites because those parasites have an increased need for highly efficient proteasomes," he said. "So, combining the proteasome inhibitor with artemisinin should make it possible to block the onset of resistance. That will, in turn, allow the continued use of that front-line malaria treatment, which has been so effective up until now."

Clinical trials of compounds derived from this research remain several years away, Bogyo cautioned.

Other Stanford co-authors are postdoctoral scholars Wouter van der Linden, PhD, Euna Yoo, PhD, and Ian Foe, PhD.

Researchers from the University of California–San Francisco and the University of Melbourne in Australia contributed to the study.

The study was funded by the National Institutes of Health; the Medical Research Council in the UK; Singapore's Agency of Science, Technology and Research; and the Netherlands Organization for Scientific Research.

Stanford's departments of Pathology and of Chemical and Systems Biology also supported the work. **ISM**

TB

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tum on demand, said research associate Tim Sweeney, MD, PhD, first author of the paper. "If someone can't produce adequate sputum, or if you have a kid who can't follow directions," it's hard to diagnose them, he said. And the sputum test is almost useless for monitoring how someone is responding to treatment. As people start to get better, they can't produce sputum for the test.

The new test developed in the Khatri lab works on an ordinary blood sample and removes the need to collect sputum. It can signal a TB infection even if the individual also has HIV. And it won't give a positive response if someone only has latent TB or has had a TB vaccine. It also doesn't matter which strain of TB has infected a person, or even if it has evolved resistance to antibiotic drugs. The test works in both adults and children.

WHO has called for a test that would give a positive result at least 66 percent of the time when a child has active TB. The Khatri test is 86 percent sensitive in children. And if the test comes up negative, it's right 99 percent of the time. That is, of 100 patients who test negative with the Khatri test, 99 do not have active TB.

The requirements of the test are simple enough that it can potentially be done under relatively basic field conditions in rural and undeveloped areas of the world. Any hospital should be able to perform the test. Villages without electricity could likely use ordinary blood samples and a solar-powered PCR machine, which multiplies strands of DNA, to accurately test people for active TB.

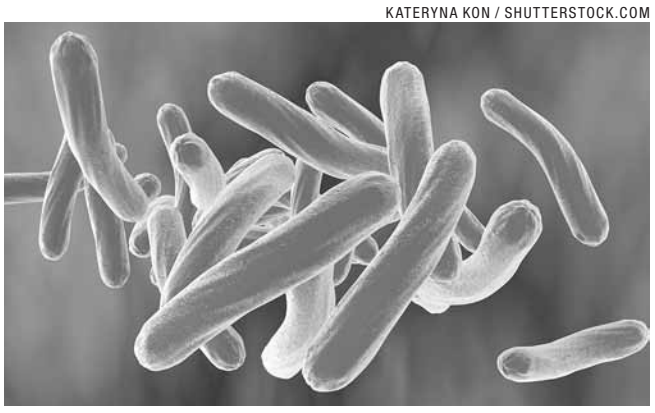
Chain reaction

When pathogens infect the cells of the body, the infection sets off a chain reaction that changes the expression of hundreds of human genes. Khatri's team identified three human genes whose expression changes in a consistent pattern, revealing the presence of an active tuberculosis infection.

The team validated the new three-gene test in a separate set of 1,400 human samples from 11 different data sets, confirming the diagnostic power of the test.

The new test not only accurately distinguishes patients who have active tuberculosis, it could also be used to monitor patients to see if they are getting better and how well they are responding to different treatments. Thus, it can be used not only for diagnosis and to inform treatment, but also to study the effectiveness of different treatments. The test's hugely accurate negative response would be especially helpful in monitoring the effectiveness of treatments during clinical trials, said Khatri.

KATERYNA KON / SHUTTERSTOCK.COM



An estimated 9.6 million people became ill with TB in 2014, and an estimated 1.5 million people died of the disease that year.

He has already begun collecting funding to develop the test for widespread use, both to diagnose TB in patients and to monitor recovery in clinical trials, allowing for more rapid development of better and cheaper treatments.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors of the paper are Cristina Tato, PhD, MPH, a research and science analyst, and Lindsay Braviak, an undergraduate student at the University of Baltimore who spent three weeks in Khatri's lab.

The research was funded by the National Library of Medicine, a Stanford Child Health Research Institute Young Investigator Award (through the Stanford Institute for Immunity, Transplantation and Infection), the Society for University Surgeons, the National Institute of Allergy and Infectious Diseases and the Bill and Melinda Gates Foundation.

Stanford's Department of Medicine also supported the work.

Sweeney is a scientific adviser to Multerra Biosciences. The three-gene set has been disclosed for possible patent protection to the Stanford Office of Technology and Licensing by Sweeney and Khatri. **ISM**

Symposium Feb. 24 on sex differences in heart health

Heart experts from across the Stanford campus will speak at a symposium on sex differences in cardiovascular health and disease Feb. 24 in Berg Hall at the Li Ka Shing Center for Learning and Knowledge.

The symposium, which is free and open to the public, will run from 1-4:30 p.m. Lunch will be provided at 12:15 p.m. For more information and to register, visit http://tinyurl.com/wsdm2016.

The event kicks off with opening remarks from Marcia Stefanick, PhD, professor of medicine and co-founder of the Stanford Women and Sex Differences in Medicine Center, and Jennifer Tremmel, MD, assistant professor of cardiovascular medicine.

Eight Stanford faculty will make presentations, including Mintu Turakhia, MD, assistant professor of cardiovascular medicine, on gender differences in quality and outcomes of care for atrial fibrillation; Patricia Nguyen, MD, assistant professor of cardiovascular medicine, on sex differences in myocardial gene expression; and Sean Wu, MD, PhD, assistant professor of cardiovascular medicine, on estrogen in viral cardiomyopathy.

The event is sponsored by the Stanford Women and Sex Differences in Medicine Center, the Stanford Cardiovascular Institute and Stanford Women's Heart Health Clinic. **ISM**

New chair of pathology department appointed, begins May 1

By Krista Conger

Thomas Montine, MD, PhD, has been appointed the new chair of the Department of Pathology at the Stanford University School of Medicine. His term will begin May 1.

He will succeed Stephen Galli, MD, a professor of pathology who has served as chair of the department since 1999.

Montine, a neuropathologist, is currently chair of pathology at the University of Washington.

"Tom is at once a distinguished investigator, an expert clinician and a respected mentor," said Lloyd Minor, MD, dean of the School of Medicine, in a statement announcing the appointment. "In the clinic and in the laboratory, Tom embodies the academic mission of Stanford Medicine as well as the creativity and collaboration that is our hallmark. He is a consummate clinician-scientist committed to our vision to lead the biomedical revolution in precision health."

Research focus on cognitive health

Montine's research focuses on the structural and molecular bases for cognitive impairment in the elderly and how they give rise to Alzheimer's disease and non-motor features of Parkinson's disease. His lab hopes to identify key pathogenic steps in these processes and to develop new ways to protect cognitive function with advancing age. Montine also directs national centers for research on Alzheimer's disease and Parkinson's disease at UW that emphasize functional genomics, early detection and the discovery of tailored therapies.

"Stanford is an amazing university that offers enormous opportunities for the next chair of pathology," said Montine. "Furthermore, the focus on precision health is one that I believe will distinguish the truly leading medical centers of the future. I am excited by the promise of the university, the School of Medicine and the vision that they are pursuing."

Thomas Montine

The goal of Stanford Medicine's focus on precision health is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

"The many individuals at Stanford Health Care and Lucile Packard Children's Hospital Stanford working to advance clinical genomics are very excited about Dr. Montine's interest and contributions in this area," said Louanne Hudgins, MD, professor of pediatrics, who was a co-leader of the search committee for the new pathology chair.

"Dr. Montine's leadership in neuropathology will provide strong synergy with Stanford's outstanding interdisciplinary program in neurological disease and the neurosciences," said Paul Khavari, MD, PhD, professor and chair of dermatology and the other co-leader of the search committee. "His expertise and leadership in clinical genomics will help accelerate efforts here to bring insights from the genome to the patient care arena. Finally, his unique combination of scientific strengths, program leadership and clinical expertise will provide the ideal set of attributes to lead Stanford's outstanding Department of Pathology into the future."

Montine is the director of the Pacific Northwest Udall Center and of the University of Washington's Alzheimer's Disease Research Center. He earned a BA in chemistry from Columbia University, a PhD in pharmacology from University of Rochester and an MD from McGill University. He completed his postgraduate medical training at Duke University before being hired as an assistant professor Vanderbilt University.

He was the 2015 president of the American Association of Neuropathologists, and he co-authored the recent National Institute on Aging-Alzheimer's Association's guidelines for the diagnosis of Alzheimer's disease. **ISM**

Peter Kim, Scott Delp elected to National Academy of Engineering

By Amy Adams

Two School of Medicine faculty members have been elected to the National Academy of Engineering: Peter Kim, PhD, professor of biochemistry, and Scott Delp, PhD, professor of bioengineering and of mechanical engineering.

Kim is now one of only 20 people who are members of all three national academies. The other two academies are the National Academy of Science and the National Academy of Medicine. Stephen Quake, PhD, professor of bioengineering and of applied physics, is also a member of all three academies.

Kim was honored for his work developing novel drugs and vaccines that are used worldwide. Before coming to Stanford in 2014, he was president of Merck Research Laboratories, where he oversaw the development of vaccines for cervical cancer, shingles and rotavirus, as well as many drugs.

Kim came to Stanford to be part of Stanford ChEM-H, an institute aimed at better understanding the chemistry of humans and developing treatments for disease. He hopes that his group will be able to contribute to the creation of an HIV vaccine. Over the past 30 years, many have tried but failed because the virus mutates so quickly. Kim's approach focuses on a highly conserved part of the virus that is only exposed as the virus is entering the cell.

Peter Kim

Scott Delp

Simulating movement

Delp was honored for his computer simulations of human movement and their applications to the treatment of clinical movement pathologies. Delp and his team have developed open-source software called OpenSim that allows scientists to create and analyze simulations of movement.

Delp recently launched the National Center for Mobility Data Integration to Insight, known as the Mobilize Center, which is a National Institutes of Health center of excellence for big data research.

The center makes use of the vast data available on movement in healthy people and in those with movement disorders and data generated through the proliferating wearable devices and phone apps that track movement, behaviors and health. **ISM**

Amy Adams is the director of interdisciplinary life sciences communications for Stanford University.

Six faculty elected fellows of medical, bioengineering institute

Six School of Medicine faculty members have been elected to the American Institute for Medical and Biological Engineering College of Fellows. Fellows are elected by their peers for their professional and public service accomplishments, research contributions and ability to serve as assets to the organization.

KWABENA BOAHEN, PhD, professor of bioengineering, uses silicon integrated circuits to emulate the brain.

Kwabena Boahen

Bruce Daniel

Karl Deisseroth

Garry Gold

Christina Smolke

Lei Xing

BRUCE DANIEL, MD, professor of radiology, researches new diagnostic and therapeutic uses for MRI, with a focus on cancer.

KARL DEISSEROTH, MD, PhD, the D.H. Chen Professor and professor of bioengineering and of psychiatry and behavioral sciences, develops techniques, including optogenetics, to examine and alter brain circuits.

CHRISTINA SMOLKE, PhD, associate professor of bioengineering, engineers functional RNAs to access and control information in genetic systems and yeast biosynthesis platforms for complex natural products.

LEI XING, PhD, the Jacob Haimson Professor and professor of radiation oncology, uses advances in engineering to enhance medical imaging and patient care in radiation oncology.

GARRY GOLD, MD, professor of radiology, uses advances in imaging technology to improve diagnosis and treatment of musculoskeletal problems. **ISM**

OF NOTE

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

TIMOTHY DURAZZO, PhD, was appointed associate professor of psychiatry and behavioral sciences, effective Nov. 1. His clinical work emphasizes the neuropsychological assessment of traumatic brain injury, Gulf War illness and neurodegenerative diseases. His research focuses on the neurological consequences of traumatic brain injury, cigarette smoking and alcohol and substance-use disorders.

MICHAEL KHODADOUST, MD, PhD, instructor in medicine, received a 2015 Young Investigator Award from the Conquer Cancer Foundation of the American Society of Clinical Oncology. The one-year grant provides $50,000. Khodadoust's research focuses on the identification of tumor antigens, with an emphasis on mantle-cell lymphoma.

Michael Khodadoust

KIM RHOADS, MD, was promoted to associate professor of surgery, effective Sept. 1. She specializes in colon and rectal surgery, and her research focuses on the connection between hospital quality and racial or ethnic disparities in cancer survival. She is the founding director of the Stanford Cancer Institute's Community Partnerships Program.

Kim Rhoads

BRENDAN VISSER, MD, was promoted to associate professor of surgery, effective Sept. 1. He specializes in hepatobiliary and pancreatic surgery. He is the medical director of the Gastrointestinal Cancers Clinical Care Program in the Stanford Cancer Center and director of the Hepatobiliary and Pancreatic Surgery Clinical Fellowship. His research focuses on treating hepatocellular carcinoma, improving technical aspects of pancreatic and liver surgery and on socioeconomic and institutional barriers to the management of hepatobiliary cancers. **ISM**

Brendan Visser