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# Johns Hopkins researchers show how a modified pacemaker strengthens failing hearts

***Findings advance opportunities for a 'pacemaker in a bottle'***

Johns Hopkins heart researchers are unraveling the mystery of how a modified pacemaker used to treat many patients with heart failure, known as cardiac resynchronization therapy (CRT), is able to strengthen the heart muscle while making it beat in a coordinated fashion. In a new study conducted on animal heart cells described in the Journal of Clinical Investigation, the scientists show that CRT changes these cells so they can contract more forcefully. The researchers also identified an enzyme that mimics this effect of CRT without use of the device.

"These discoveries potentially give us new pathways to benefit more heart failure patients - not only those whose hearts beat out of sync, but also those who currently do not qualify for CRT therapy yet still need an effective treatment to help their heart pump stronger," says David Kass, M.D., professor of medicine and biomedical engineering at the Johns Hopkins University School of Medicine and senior author of the study. "Understanding the inner workings of CRT at the biological level may lead, in essence, to a 'pacemaker in a bottle.'"

The researchers say their ultimate goals are to develop drugs or genetic therapies that strengthen failing hearts and to design a test to identify patients who would be most likely to benefit from CRT.

Kass explains that while the typical implanted pacemaker has only one wire that stimulates the right side of the heart, the CRT pacemaker has two wires. The second wire goes to the surface of the left side of the heart to enable both sides of the heart to be stimulated together. CRT helps people whose hearts beat out of sync - one side is activated to "beat" before the other, preventing the muscle from pumping blood evenly. This condition is known as dyssynchrony. CRT "paces" the rhythms of both sides to restore a coordinated beat.

In their experiments, the researchers used an animal model of heart failure with dyssynchrony and also examined the impact of CRT on the heart. By studying isolated muscle tissue and muscle cells, they examined the relationship between contraction and the calcium that triggers it. In the hearts that beat out of sync, force from the muscle cells and the level of calcium needed to generate contractions were very much reduced. CRT improved contraction force more than calcium, and this led to the discovery that CRT had increased the sensitivity of the muscle to calcium.

The next question was how this change had occurred. Calcium sensitivity is a property of the proteins that form the contracting "engine" of muscle, so the investigators examined how these proteins had been biochemically altered by CRT. After ruling out all the known ways this might have occurred, they turned to a newer approach, testing for changes in more than 150 proteins and discovered that CRT specifically modified 13 of them.

"Once we discovered which proteins were being altered, we were able to identify an enzyme likely responsible for these changes," noted lead author Jonathan Kirk, Ph.D., a post-doctoral fellow at the Johns Hopkins University School of Medicine. Working with heart muscle and isolated cells from the same animal models, the researchers found that the enzyme turned out to be GSK-3 beta, which was able to convert the behavior of muscle cells from a heart that was beating out of sync to what looked like heart cells that had received CRT, essentially mimicking the effect of CRT.

In further lab experiments, Kass and his colleagues found that although GSK-3 beta was inactive in muscle from a failing and dyssynchronous heart, it was reactivated by CRT. When that happened, the enzyme altered the motor proteins so that they generated greater force using the same amount of calcium-based activation.

"It had never been shown before that GSK-3 beta could modify motor proteins in the heart to make them more sensitive to calcium. It is surprising that this same type of effect can be produced by a pacemaker therapy like CRT," says Kass.

Nearly all existing medications for heart failure increase heart contraction by enhancing levels of calcium available to muscle cells, but over time, these higher levels can be toxic to the heart.

Altering the calcium sensitivity of the muscle is not the only way CRT can improve heart function. In a study published in 2011, Kass and colleagues also showed that CRT enables heart muscle to respond to hormones, such as adrenaline, which stimulates pumping ability, in a similar way to what happens during exercise.

The Kass Lab played a key role in developing CRT for use in patients in the late 1990s. The Food and Drug Administration approved CRT in 2001, and it is widely used today to improve symptoms and help people live longer.

In an unusual twist to the way therapies are usually developed, CRT was first tested in patients, but the biological mechanisms as to why it worked were not understood. The new work is running the discovery clock backwards, revealing these mechanisms and their potential to benefit many patients with heart failure.

*In addition to Kass and Kirk, other authors on the study were: Ronald J. Holewinski, Viola Kooij, Wei Dong Gao and Jennifer Van Eyk from the Johns Hopkins University School of Medicine; Giulio Agnetti from the University of Bologna; and Richard S. Tunin, Namthip Witayavanitkul and Pieter P. de Tombe from the Stritch School of Medicine at Loyola University, Chicago. Here is a link to the full study article: http://www.jci.org/articles/view/69253?key=fdd04e03e5fcde1d87d4*

***http://www.eurekalert.org/pub_releases/2013-12/wtsi-wmt112913.php***

## What makes the deadliest form of malaria specific to people?

***The biological interactions that make some malaria parasites specific to host species***

Researchers have discovered why the parasite that causes the deadliest form of malaria only infects humans. The team recently showed that the interaction between a parasite protein called RH5 and a receptor called basigin was essentially required for the invasion of red blood cells by the parasite that causes the deadliest form of malaria. Now, they've discovered that this same interaction is also an important factor in explaining why the parasite seems to be remarkably specific to humans. This research will help guide eradication strategies in regions where malaria is endemic.

There are several distinct species of parasite that cause malaria. The malaria parasite species responsible for severe illness and death, Plasmodium falciparum, only infects humans, but is closely related to several species that infect chimpanzees and gorillas. Strangely, these species seem to be very specific – individual species appear to infect only humans, chimpanzees or gorillas, even when these primates live in close proximity. This striking observation piqued the curiosity of the team which prompted a search for the molecules that controls this specificity and revealed the important role of the RH5-basigin interaction.

"It's remarkable that the interaction of a single pair of proteins can explain why the most deadly form of malaria is specific to humans" says Dr Julian Rayner, from the Wellcome Trust Sanger Institute Malaria Programme. "This research will strengthen eradication strategies by ruling out great apes as possible reservoirs of human infection by P. falciparum."

The team investigated the question of host specificity by examining two important protein interactions involved in the invasion of red blood cells - the interactions between the parasite and host EBA175-Glycophorin A and RH5-basigin. They found that the EBA175 protein from chimpanzee specific malaria parasites could bind to human Glycophorin A, thereby ruling out this interaction as a specificity factor. However, the RH5 protein from P. falciparum did not bind to the gorilla basigin protein and only bound extremely weakly to chimpanzee basigin. Therefore, the species specificity of this interaction mirrored the known infection profile of P. falciparum and provided a molecular explanation for why P. falciparum only infects humans.

"This interaction seems to explain why P. falciparum only infects people and not apes," says Professor Beatrice Hahn, author from the University of Pennsylvania. "This may also be an important guiding factor in the development of eradication strategies for the elimination of P. falciparum in endemic areas."

Until recently, studying protein interactions between the malaria parasite and great apes has been challenging. Both chimpanzees and gorillas are protected species and so obtaining blood samples that would help answer these questions is incredibly difficult.

"Today, we can produce these proteins synthetically in the laboratory to avoid the use of blood samples from endangered animals," says Dr Gavin Wright, lead author from the Wellcome Trust Sanger Institute. "In time, these scientific advances will lead to improved treatments, eradication strategies and, vaccine development for one of the world's major health problems."

*Madushi Wanaguru, Weimin Liu, Beatrice H. Hahn, Julian C. Rayner, and Gavin J. Wright. (2013) 'RH5–Basigin interaction plays a major role in the host tropism of Plasmodium falciparum'*
*Advanced online publication in PNAS 02 Dec 2013. http://www.pnas.org/cgi/doi/10.1073/pnas.1320771110*
*This work was supported by the Wellcome Trust, Medical Research Council, the University of Pennsylvania Center for AIDS Research Single Genome Amplification Core Facility, and National Institutes of Health.*

***http://www.eurekalert.org/pub_releases/2013-12/foas-nrs120213.php***

## New research shows obesity is an inflammatory disease

***New research in The FASEB Journal suggests that an abnormal amount of an inflammatory protein called PAR2 is present on abdominal fat tissues of overweight and obese humans and rats***

Bethesda, MD - Scientists have moved a step closer to an "obesity drug" that may block the effects of diets high in sugar and fats. In a new research report published in the December 2013 issue of The FASEB Journal, scientists show that there is an abnormal amount of an inflammatory protein called PAR2 in the abdominal fat tissue of overweight and obese humans and rats. This protein is also increased on the surfaces of human immune cells by common fatty acids in the diet. When obese rats on a diet high in sugar and fat were given a new oral drug that binds to PAR2, the inflammation-causing properties of this protein were blocked, as were other effects of the high-fat and high-sugar diet--including obesity itself.

"This important new finding links obesity and high fat high sugar diets with changes in immune cells and inflammatory status, highlighting an emerging realization that obesity is an inflammatory disease," said David P. Fairlie, Ph.D., study author from the Institute for Molecular Bioscience at the University of Queensland, in Bribane, Australia. "Drugs designed to block certain inflammatory proteins, as in this report, may be able to prevent and treat obesity, which in turn is a major risk factor for type 2 diabetes, heart disease, stroke, kidney failure, limb amputation, and cancers."

To make this discovery, Fairlie and colleagues discovered the first potent, selective and orally bioavailable small molecule antagonists of PAR2 and characterized their functional responses in inflammatory cellular and animal models. They found that PAR2 expression is increased in vivo in adipose tissue from obese humans and rats, stimulated in vitro in human macrophages by the dietary fatty acid palmitic acid, and inhibited in vivo and in vitro by a PAR2 antagonist. This antagonist was then used as a tool to dissect roles for PAR2 activation in mediating metabolic dysfunction in human monocyte-derived macrophages (HMDM), human and rodent adipocytes, and diet-induced obesity in rats. Oral treatment of diet-induced obese rats attenuated PAR2 signaling in adipose tissue and inhibited adipose inflammation, insulin resistance, diet-induced obesity and cardiovascular abnormalities. This is the first report that a PAR2 antagonist improves obesity, glucose homeostasis and obesity-associated chronic inflammation in vivo. These findings indicate that increased PAR2 expression may be a valuable new biomarker for metabolic dysfunction and further, that PAR2 antagonism can be an effective intervention for treating metabolic dysfunction and obesity.

"We know that that eating too much and not exercising enough makes you overweight, and then obese, but why? The bottom line of this report is that obesity is an inflammatory disease, and inflammation plays a greater role in the downward spiral to obesity than most people realize." said Gerald Weissmann, M.D., Editor-in-Chief of The FASEB Journal. "It appears that once we can control the inflammation, we can begin to get everything else in line. Fortunately, these scientists have already identified one promising compound that seems to work."

*Details: Junxian Lim, Abishek Iyer, Ligong Liu, Jacky Y. Suen, Rink-Jan Lohman, Vernon Seow, Mei-Kwan Yau, Lindsay Brown, and David P. Fairlie. Diet-induced obesity, adipose inflammation, and metabolic dysfunction correlating with PAR2 expression are attenuated by PAR2 antagonism. FASEB J December 2013 27:4757-4767, doi:10.1096/fj.13-232702 ; http://www.fasebj.org/content/27/12/4757.abstract*

***http://www.eurekalert.org/pub_releases/2013-12/epfd-tnh120313.php***

## Tuberculosis: Nature has a double-duty antibiotic up her sleeve

***A natural antibiotic turns out to be a lethal weapon in the fight against tuberculosis.***

Scientists have discovered it has an unexpected dual action that dramatically reduces the probability that TB bacteria will become resistant

Technology has made it possible to synthesize increasingly targeted drugs. But scientists still have much to learn from Mother Nature. Pyridomycin, a substance produced by non-pathogenic soil bacteria, has been found to be a potent antibiotic against a related strain of bacteria that cause tuberculosis. The EPFL scientists who discovered this unexpected property now have a better understanding of how the molecule functions. Its complex three-dimensional structure allows it to act simultaneously on two parts of a key enzyme in the tuberculosis bacillus, and in doing so, dramatically reduce the risk that the bacteria will develop multiple resistances. The researchers, along with their colleagues at ETH Zurich, have published their results in the journal Nature Chemical Biology.

Stewart Cole, director of EPFL's Global Health Institute, led a team that discovered the anti-tuberculosis effect of pyridomycin in 2012. By inhibiting the action of the "InhA" enzyme, pyridomycin literally caused the thick lipid membrane of the bacterium to burst. Now the scientists understand how the molecule does this job.

**Dual anti-mutation ability**

The tuberculosis bacillus needs the InhA enzyme along with what scientists refer to as a "co-factor," which activates the enzyme, in order to manufacture its membrane. The scientists discovered that pyridomycin binds with the co-factor, neutralizing it.

But pyridomycin doesn't stop there. It also blocks another element needed for making the membrane, the InhA binding site. "Researchers in the pharmaceutical industry have been looking for this weakness in the TB bacillus for decades," explains Ruben Hartkoorn, first author on the article.

By binding simultaneously onto these two elements and neutralizing them, pyridomycin prevents the bacterium from generating its membrane, and it ends up bursting like a balloon. Better still, this dual action drastically reduces the risk that the bacteria will become resistant, because in order to develop resistance, two different specific mutations must exist at the same time. This is increasingly important because cases of multi-resistant TB are on the rise.

**Nature's twisting paths – a lesson in efficiency**

"It's a powerful lesson from nature with respect to drug design," explains Cole, co-author and EPFL professor. "The three-dimensional structures of naturally occurring molecules are often more complex, more twisted, than synthetic molecules, and that's precisely what allows pyridomycin to bind onto these two sites simultaneously." In fact, it binds so effectively that the molecule is not yet ready to be used therapeutically: it doesn't last long enough in the patient's body. This is the point at which bioengineering needs to take over from Mother Nature – to develop a more robust version of the molecule. This is what the ETH team led by Karl-Heinz Altmann is working on. "Eventually we could multiply the molecule's binding sites, so that it could inhibit critical functions of other pathogenic bacteria," says Cole.

***http://bit.ly/1blw6vj***

## Turning the Moon into a Giant Space Solar Power Hub

***When it comes to space and energy, we need to think big. That's what one Japanese company is doing - and they're reaching for the moon, literally.***

**Dec 3, 2013 04:27 AM ET // by Ian O'Neill**

The best thing about the moon is that one lunar hemisphere is constantly bathed in sunlight (except for the occasional eclipse), so using solar arrays to generate power may not seem like such a stretch. Take China's recently-launched Chang'e 3 Yutu rover for example, it's solar powered. Also, Apollo astronauts set up solar-powered experiments on the lunar regolith. But how about wrapping the moon's equator in a 250 mile wide band of solar panels and beaming the power generated back to Earth?

That's exactly what Shimizu Corporation is proposing and they reckon their concept could harness a steady stream of 13,000 terawatts of power. According to Business Insider, "the total installed electricity generation summer capacity in the United States was 1,050.9 gigawatts." Such a vast energy resource could be transformative for our civilization. As Obi-Wan might say: "That's no moon. It's a space (solar power) station."

"A shift from economical use of limited resources to the unlimited use of clean energy is the ultimate dream of all mankind," says the company's website. "The LUNA RING, our lunar solar power generation concept, translates this dream into reality through ingenious ideas coupled with advanced space technologies."

Indeed, advanced space technologies will be needed, not only to harvest solar energy and efficiently beam it back to Earth, but its very construction will require several leaps in robotic technology development. Also, this mother of all engineering tasks will need to see some significant changes in international space treaties before it sees light of day.

Resembling a moon born from science fiction, the LUNA RING is just that, a ring around the moon. The ring, stretching 6,800 miles around the moon's circumference, will be constructed by robots that will "perform various tasks on the lunar surface, including ground leveling and excavation of hard bottom strata." The entire project will be overseen by a team of humans while the bulk of the robotic tasks can be teleoperated from Earth.

It's all very well building a huge array of solar panels around the moon, but how would the power be sent to Earth? As our atmosphere is virtually transparent to microwaves and lasers, Shimizu envisages solar energy being fed through microwave/laser transmitters located around the Earth-facing side of the moon. As the moon orbits the Earth and the Earth rotates, international receiving stations will feed electricity grids with plentiful lunar solar power as the moon rises to when it sets.

The designers are keen to point out that this is a green energy resource that could benefit the whole of mankind. What's more, when the infrastructure is set up, other resources can be exploited - such as mining for precious minerals and fabricating products from regolith. One could imagine an international consortium of nations and/or companies that buy a stake in the LUNA RING to aid its construction. Each partner would then have rights to construct receiving stations in their geographical location of choice, weaning us off polluting sources of power. Japan, which was hurt by the devastating Fukushima meltdown in 2011, is actively seeking out alternative power resources to wean itself off nuclear energy - it doesn't get more "alternative" than this.

Shimizu isn't suggesting we can build the LUNA RING now - they propose 2035 as the target start date. By that time, they assume that the technology behind space solar power - orbiting solar arrays that beam power to Earth via microwave transmitters - will have matured and we should have a sufficient in-space infrastructure to support such a project. Worrying about small practical details - such as how the LUNA RING solar panels will be cleaned and whether or not the international community would support such a plan - seems a little premature.

The project may seem a little "out there," but assuming sufficiently developed current technologies, it could be done. Sure, it would be the biggest engineering task humans have ever undertaken, but it's not out of line with what we'd envisage an advanced civilization to construct.

We would be well on our way to becoming a Type I civilization on the Kardashev scale if we could accomplish such a grand feat. The Kardashev scale is a well-known measure of a civilization's technological development.

We are currently a Type 0; we have a very limited ability of harnessing global energy supplies. Should we reach a Type I, we will be adept at utilizing all of the energy available on Earth. So, if we were to set up a space solar power hub on the very useful natural satellite in orbit around our planet, we are bound to get a Kardashev-sized boost in the civilization stakes.
It may only be a concept, but it's not hard to see how the LUNA RING could undergo some iterative steps to eventually become a reality. And sometimes, you have to think really big to confront some of the biggest challenges facing our species.

http://www.eurekalert.org/pub_releases/2013-12/f-dod120213.php

## Domestication of dogs may have elaborated on a pre-existing capacity of wolves to learn from humans

***Wolves can learn from observing humans and pack members where food is hidden and recognize when humans only pretend to hide food, reports a study for the first time in the open-access journal Frontiers in Psychology.***

These findings imply that when our ancestors started to domesticate dogs, they could have built on a pre-existing ability of wolves to learn from others, not necessarily pack members.
A paper published recently in the journal Science suggested that humans domesticated dogs about 18 thousand years ago, possibly from a European population of grey wolves that is now extinct. But it remains unknown how much the ability of dogs to communicate with people derives from pre-existing social skills of their wolf ancestors, rather than from novel traits that arose during domestication.
In a recent study, Friederike Range and Zsófia Virányi from the Messerli Research Institute at the University of Veterinary Medicine Vienna investigated if wolves and dogs can observe a familiar "demonstrator" – a human or a specially trained dog – to learn where to look for food within a meadow. The subjects were 11 North American grey wolves and 14 mutts, all between 5 and 7 months old, born in captivity, bottle-fed, and hand-raised in packs at the Wolf Science Center of Game Park Ernstbrunn, Austria.
The wolves and dogs were two to four times more likely to find the snack after watching a human or dog demonstrator hide it, and this implies that they had learnt from the demonstration instead of only relying on their sense of smell. Moreover, they rarely looked for the food when the human demonstrator had only pretended to hide it, and this proves that they had watched very carefully.
The wolves were less likely to follow dog demonstrators to hidden food. This does not necessarily mean that they were not paying attention to dog demonstrators: on the contrary, the wolves may have been perceptive enough to notice that the demonstrator dogs did not find the food reward particularly tasty themselves, and so simply did not bother to look for it.
The researchers conclude that the ability to learn from other species, including humans, is not unique to dogs but was already present in their wolf ancestors. Prehistoric humans and the ancestors of dogs could build on this ability to better coordinate their actions.
*1. For a copy of the embargoed paper, please contact Gozde Zorlu: gozde.zorlu@frontiersin.org*
*2. Videos and images are available from this link: https://www.dropbox.com/sh/uhpvshob6i8g0td/hkBXY0xaIJ*
*3. Please refer to the source of publication, Frontiers in Psychology, and for online articles, please include a link to the study: http://www.frontiersin.org/Journal/10.3389/fpsyg.2013.00868/abstract*
*Article title: Observing humans and conspecifics: social learning in dogs and wolves Journal: Frontiers in Psychology DOI: 10.3389/fpsyg.2013.00868*

http://www.eurekalert.org/pub_releases/2013-12/cums-frf120213.php

## First real-time flu forecast successful

***Researchers take a page from weather forecasting to predict seasonal influenza outbreaks in 108 cities across the country***

Scientists were able to reliably predict the timing of the 2012-2013 influenza season up to nine weeks in advance of its peak. The first large-scale demonstration of the flu forecasting system by scientists at Columbia University's Mailman School of Public Health was carried out in 108 cities across the United States.
Results are published online in the journal Nature Communications.
The flu forecasting system adapts techniques used in modern weather prediction to turn real-time, Web-based estimates of influenza infection into local forecasts of the seasonal peak by locality. Influenza activity peaked in cities in the southeast as early as December 2012, but crested in most of the country in the first weeks of 2013.
Year to year, the flu season is highly variable. It can happen anywhere from December to April. But when it arrives, cities can go from practically no cases to thousands in a very short time. "Having greater advance warning of the timing and intensity of influenza outbreaks could prevent a portion of these influenza infections

by providing actionable information to officials and the general public," says first author Jeffrey Shaman, PhD, assistant professor of Environmental Health Sciences at Columbia University's Mailman School of Public Health.

For the public, the flu forecast could promote greater vaccination, the exercise of care around people sneezing and coughing, and a better awareness of personal health. For health officials, it could inform decisions on how many vaccines and antiviral drugs to stockpile, and in the case of a virulent outbreak, whether other measures, like closing schools, are necessary.

**Study Results**

The new study builds on the researchers' 2012 study that used the system to retrospectively predict the peak of the flu in New York City for the years 2003-2008. That research was limited to one city and performed as a test of the system. The current study is the first to make predictions in actual real-time and for the whole country. Beginning in late November of 2012, the researchers used the flu forecasting system to perform weekly estimates for 108 cities. They shared the results with the CDC and posted them online in an academic archive. Near the end of 2012, four weeks into the flu season, the system had predicted 63% of cities accurately. As the season progressed, the accuracy increased. By week four, it successfully predicted the seasonal peak in 70% of the country. It was able to give accurate lead-times up to nine weeks in advance of the peak; most lead-times were two to four weeks.

The flu forecasts were also much more reliable than those made using alternate, approaches that rely on historical data. "Our method greatly outperformed these alternate schemes," says Dr. Shaman.

The researchers saw regional differences in the accuracy of the system, but they were likely within normal variation. "As an example, retrospectively, we've been able to predict the flu in Chicago very well; this year we did a terrible job in that city. For other cities, the opposite held. It averages out. On the whole the system performed very well," Dr. Shaman says. However, there were hints of geographical differences. "We were able make better predictions in smaller cities. Population density may also be important. It suggests that in a city like New York, we may need to predict at a finer granularity, perhaps at the borough level. In a big sprawling city like Los Angeles, we may need to predict influenza at the level of individual neighborhoods."

Google Flu Trends Goes "Off the Rails"

The researchers designed the flu forecasting system to use combined data from 1) Google Flu Trends, which makes estimates of outbreaks based on the number of flu-related search queries, and 2) region-specific reports from the Centers for Disease Control on verified cases of flu. The system approach is analogous to weather forecasting, which employs real-time observational data to reduce model forecasts error. In the last year, the researchers slightly modified the system to be more representative of flu rather than flu and other respiratory problems. Nevertheless, there was unusual level of "noise" in the data related to problems with Google Flu Trends.

How did this happen? One explanation is the high number of media stories about the flu, including some about the flu forecasting system itself. The result was a spike in people using Google to research the flu, which could have overloaded the Flu Trends algorithm. It's an irony not lost on Dr. Shaman. "There was a tremendous amount of media attention accorded to the flu last year. I was part of the problem myself," he says. Another factor may have been the particular strain of flu in circulation. "The flu was very virulent and was making people very sick, more so than previous seasons," says Dr. Shaman. Again this could have led to spike in flu-related Google search queries. (In October, Google announced that it has revised the Flu Trends, which Dr. Shaman hopes will make flu forecasting more accurate.)

The system will be put back in action as soon as the flu season begins again. "Right now there are few cases of the flu, but as soon as the needle starts to move, we will start making predictions," says Dr. Shaman. This season the forecasts will be more readily available to the public on a website hosted by Columbia's Mailman School of Public Health expected to launch in the coming weeks.

Worldwide, influenza kills an estimated 250,000 to 500,000 people each year, according to the World Health Organization. In the U.S. 3,000-49,000 die from the flu every year, and about 45% of Americans were vaccinated for the flu, according to the CDC.

*Co-authors include Wan Yang and James Tamerius, post-doctoral students of Dr. Shaman (Dr. Tamerius is currently at the University of Iowa); Alicia Karspeck at the National Center for Atmospheric Research; and Marc Lipsitch at the Harvard School of Public Health.*

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http://www.eurekalert.org/pub_releases/2013-12/asfm-tcd120313.php

## Toxigenic C. difficile resides harmlessly in infants, poses risk to adults

***Infants frequently carry Clostridium difficile with no harm to themselves but can spread the bacteria to adults***

Infants and toddlers frequently carry toxigenic Clostridium difficile, usually with no harm to themselves, but can serve as a reservoir and spread the bacteria to adults in whom it can cause severe disease, according to a study by a team of Swedish researchers published ahead of print in the Journal of Clinical Microbiology.

In the study, which involved following 42 children from birth to 1 ½ or 3 years, the investigators found that C. difficile strains persisted for more than six months in roughly one third of such infants. A majority of the persistant colonizations belonged to either of two toxigenic ribotypes which both have commonly been isolated from adult and elderly people with C. difficile toxin-mediated disease in Sweden and in other countries.

Previous studies from the 1980s found that the rate of colonization peaked during the first six months of life, and then declined, as the gut microbiota became more complex. A 2000 study by the current study author found that colonization by C. difficile kept rising until about a year of age.

"We think that this is the result of an impoverishment of the gut flora, that infants have fewer types of bacteria in their gut, compared to 30 years ago," says first author Ingegerd Adlerberth, of the University of Gothenberg, Sweden. "It is known that gut microbiota of high complexity suppresses C. difficile growth and toxin production. That is why treatment with broad-spectrum antibiotics is a risk factor for C. difficile disease."

The paper concludes with a warning that the prevalence of toxigenic C. difficile bacteria in the gut of infants and young children "provides ample opportunity for spread to individuals at risk for C. difficile disease."

C. difficile disease has been notoriously hard to treat in the elderly, who often undergo numerous courses of antibiotics without eliminating the disease. Recently, a still highly experimental treatment, fecal transplant, has proven far more successful. That treatment involves taking fecal material from a healthy person, and inserting it into the diseased patient's colon.

*A copy of the manuscript can be found online at http://bit.ly/asmtip1213a. The article is scheduled for formal publication in the January 2014 issue of the Journal of Clinical Microbiology.*

http://www.eurekalert.org/pub_releases/2013-12/cfaa-arg120313.php

## Alzheimer's risk gene may begin to affect brains as early as childhood, CAMH research shows

***People who carry a high-risk gene for Alzheimer's disease show changes in their brains beginning in childhood, decades before the illness appears, new research from the Centre for Addiction and Mental Health (CAMH) suggests.***

Toronto - The gene, called SORL1, is one of a number of genes linked to an increased risk of late-onset Alzheimer's disease, the most common form of the illness. SORL1 carries the gene code for the sortilin-like receptor, which is involved in recycling some molecules in the brain before they develop into beta-amyloid a toxic Alzheimer protein. SORL1 is also involved in lipid metabolism, putting it at the heart of the vascular risk pathway for Alzheimer's disease as well.

"We need to understand where, when and how these Alzheimer's risk genes affect the brain, by studying the biological pathways through which they work," says Dr. Aristotle Voineskos, head of the Kimel Family Translational Imaging-Genetics Laboratory at CAMH, who led the study. "Through this knowledge, we can begin to design interventions at the right time, for the right people."

The study was recently published online in Molecular Psychiatry with Dr. Voineskos's graduate student, Daniel Felsky as first author, and was a collaborative effort with the Zucker Hillside Hospital/Feinstein Institute in New York and the Rush Alzheimer's Disease Center in Chicago.

To understand SORL1's effects across the lifespan, the researchers studied individuals both with and without Alzheimer's disease. Their approach was to identify genetic differences in SORL1, and see if there was a link to Alzheimer's-related changes in the brain, using imaging as well as post-mortem tissue analysis.

In each approach, a link was confirmed.

In the first group of healthy individuals, aged eight to 86, researchers used a brain imaging technique called diffusion tensor imaging (DTI). Even among the youngest participants in the study, those with a specific copy of SORL1 showed a reduction in white matter connections in the brain important for memory performance and executive function.

The second sample included post-mortem brain tissue from 189 individuals less than a year old to 92 years, without Alzheimer's disease. Among those with that same copy of the SORL1 gene, the brain tissue showed a disruption in the process by which the gene translated its code to become the sortilin-like receptor.

Finally, the third set of post-mortem brains came from 710 individuals, aged 66 to 108, of whom the majority had mild cognitive impairment or Alzheimer's. In this case, the SORL1 risk gene was linked with the presence of amyloid-beta, a protein found in Alzheimer's disease.
Dr. Voineskos notes that risk for Alzheimer's disease results from a combination of factors – unhealthy diet, lack of exercise, smoking, high blood pressure combined with a person's genetic profile – which all contribute to the development of the illness. "The gene has a relatively small effect, but the changes are reliable, and may represent one 'hit', among a pathway of hits required to develop Alzheimer's disease later in life".
While it's too early to provide interventions that may target these changes, "individuals can take measures in their own lifestyle to reduce the risk of late-onset Alzheimer's disease." Determining whether there is an interaction with this risk gene and lifestyle factors will be one important next step.
In order to develop genetically-based interventions to prevent Alzheimer's disease, the biological pathways of other risk genes also need to be systematically analyzed, the researchers note.
This research does, however, build on a previous CAMH imaging-genetics study on another gene related to Alzheimer's disease. That study showed that a genetic variation of brain-derived neurotrophic factor (BDNF) affected brain structures in Alzheimer's.
"The interesting connection is that BDNF may have important therapeutic value. But there is data to suggest that the effects of BDNF won't work unless SORL1 is present, so there is the possibility that if you boost the activity of one gene, the other will increase," says Dr. Voineskos, adding that BDNF therapeutics are in development. A next stage in the research, he says, is to look at the interaction of BDNF and SORL1.

***http://bit.ly/1iIlAVJ***

## Hong Kong gets its first case of deadly H7N9 bird flu

***Deadly bird flu is on the march. A 35-year old woman has become the first person in Hong Kong to contract the H7N9 virus, a sign that it is spreading across China.***

**17:31 03 December 2013 by Debora MacKenzie**

The woman, a domestic worker, is in a critical condition in hospital. The family she works for was under quarantine with mild flu symptoms. It is thought that she caught the virus from a chicken that she killed, cooked and ate in Shenzhen, which lies in the neighbouring Guangdong province.
H7N9 spreads "silently" in poultry, which show no symptoms but can transmit the virus to humans. People in very close contact can sometimes pass it to one another.
The virus first broke out in people earlier this year, much further north in Shanghai. Back then, it infected 134 and killed 45. Infections stopped during the summer but autumn has seen four so far, including the most recent, the woman in Hong Kong.
Hong Kong has now stopped importing Shenzhen chickens and is screening people at its border. Shanghai also announced this week that for the next five years it will shut all live markets from February to April, when millions travel to celebrate new year.

***http://www.space.com/23814-alien-planets-water-hubble-telescope.html***

## Signs of Water Found on 5 Alien Planets by Hubble Telescope

***NASA scientists found faint signatures of water in the atmospheres of five distant planets. All five planets appear to be hazy.***

**By Mike Wall, Senior Writer | December 03, 2013 02:54pm ET**

NASA's Hubble Space Telescope has detected water in the atmospheres of five planets beyond our solar system, two recent studies reveal.
The five exoplanets with hints of water are all scorching-hot, Jupiter-size worlds that are unlikely to host life as we know it. But finding water in their atmospheres still marks a step forward in the search for distant planets that may be capable of supporting alien life, researchers said.
"We're very confident that we see a water signature for multiple planets," Avi Mandell, of NASA's Goddard Space Flight Center in Greenbelt, Md., lead author of one of the studies, said in a statement. "This work really opens the door for comparing how much water is present in atmospheres on different kinds of exoplanets — for example, hotter versus cooler ones."
The two research teams used Hubble's Wide Field Camera 3 to analyze starlight passing through the atmospheres of the five "hot Jupiter" planets, which are known as WASP-17b, HD209458b, WASP-12b, WASP-19b and XO-1b. The atmospheres of all five planets showed signs of water, with the strongest signatures found in the air of WASP-17b and HD209458b.
"To actually detect the atmosphere of an exoplanet is extraordinarily difficult. But we were able to pull out a very clear signal, and it is water," Drake Deming of the University of Maryland, lead author of the other recent study, said in a statement.

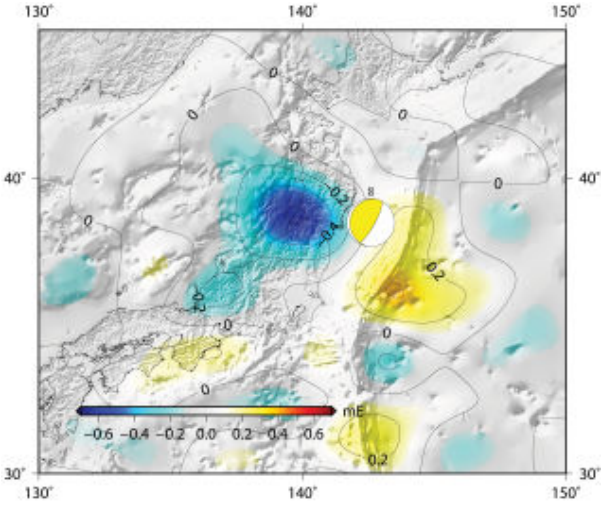
Water is thought to be a common constituent of exoplanet atmospheres and has been found in the air of several other distant worlds to date. But the new work marks the first time scientists have measured and compared profiles of the substance in detail across multiple alien worlds, researchers said.
Astronomers track the planet as it passes in front of its host star and study which wavelengths of light are absorbed. The water signatures were less intense than expected in all cases, likely because the five hot Jupiters are surrounded by a haze of dust, researchers said.
"These studies, combined with other Hubble observations, are showing us that there are a surprisingly large number of systems for which the signal of water is either attenuated or completely absent," Heather Knutson of the California Institute of Technology in Pasadena, a co-author on Deming's paper, said in a statement. "This suggests that cloudy or hazy atmospheres may in fact be rather common for hot Jupiters."
The study led by Mandell came out today (Dec. 3) in The Astrophysical Journal, while the paper led by Deming was published in September in the same journal.

***http://phys.org/news/2013-12-earthquake-scars-earth-gravity.html***

## Earthquake scars Earth's gravity

***Earth's gravity scarred by earthquake***

Phys.org - ESA's GOCE satellite has revealed that the devastating Japanese earthquake of 2011 left its mark in Earth's gravity – yet another example of this extraordinary mission surpassing its original scope.
GOCE mapped Earth's gravity with unrivalled precision for over four years, but nobody really expected the data to show changes over time. Now, careful analysis shows the effects of the 9.0 earthquake that struck east of Japan's Honshu Island on 11 March 2011 are clearly visible in GOCE's gravity data.
Large earthquakes not only deform Earth's crust, but can also cause tiny changes in local gravity. The strength of gravity varies from place to place on our planet's surface and it was GOCE's task to map these variations very precisely.




***Gravity scar over Japan.*** **Credit: DGFI/TU Delft**

There are a number of reasons why values of gravity differ, but one is a consequence of material inside Earth being inhomogeneous and unevenly distributed. Since earthquakes shift around rock and other material tens of km below the surface, they also cause small changes in the local gravity. Earthquakes under oceans, as in the 2011 Japanese quake, can also change the shape of the sea bed. This displaces water and changes the sea level, which in turn also affects gravity.
After more than doubling its planned life in orbit, the satellite recently ran out of fuel and reentered the atmosphere, largely disintegrating in the process. Although it is no longer in orbit, the real mission is only just starting because scientists will be analysing the data for years to come to help understand many aspects of our world.
Information from GOCE is being used to understand how oceans transport huge quantities of heat around the planet and to develop a global height reference system, for example. The mission has already shed new light on different aspects of Earth – from atmospheric density and winds, to mapping the boundary between the crust and upper mantle, and to understand geodynamic processes occurring in these layers far below our feet.
In a surprising discovery earlier this year unrelated to gravity changes, the satellite's accelerometer and ion thruster also revealed that GOCE had 'felt' sound waves in space from the Japanese quake.
Recently, scientists from the German Geodetic Research Institute, DGFI, and from Delft University of Technology in the Netherlands analysed the high-resolution vertical gravity gradients measured over Japan. They discovered that the quake had clearly ruptured the gravity field.
This is the first time that GOCE has been shown to have found changes over time. This work was carried out through ESA's Earth Observation Support to Science Element. Moreover, the gravity change measured by GOCE differs in size and location compared to those predicted by standard models.
GOCE's results are consistent with coarser observations from the NASA–German Grace satellite, which is designed to measure changes over time. This suggests that GOCE data will be important in improving models and will therefore contribute to our understanding of earthquakes.
Martin Fuchs from DGFI said, "Thus, we see that GOCE gravity gradients complement other types of data such as seismic, GPS and GRACE satellite gravimetry. "We are now working in an interdisciplinary team to

combine GOCE data with other information to obtain a better picture of the actual rupture in the gravity field than is currently available."

***http://phys.org/news/2013-12-rapid-climate-year-lag.html***

## Rapid climate changes, but with a 120 year time lag

***Geoscientists report a rapid climate change occurred in different regions with a time difference of 120 years***

Regional climate changes can be very rapid. A German-British team of geoscientists now reports that such a rapid climate change occurred in different regions with a time difference of 120 years. Investigation in the west German Eifel region and in southern Norway demonstrated that at the end of the last glaciation about 12,240 years before present climate became warmer, first recognised in the Eifel region and 120 years later in southern Norway. Nonetheless, the warming was equally rapid in both regions.

The team around Christine Lane (Oxford University) and Achim Brauer from the GFZ German Research Centre for Geosciences reports in the latest volume of Geology that within the younger Dryas, the last about 1100-year long cold phase at the end of the last ice age, a rapid warming first was measured in the Eifel region. Sediment cores from the Meerfelder Maar lake depict a typical deposition pattern, which was also found in the sediments of Lake Krakenes in southern Norway, but with a time lag of 120 years.

But how did the researcher revealed such a accurate time marking? "12 140 years ago a major eruption of the Katla volcano occurred on Iceland" explains Achim Brauer. "The volcanic ash was distributed by strong winds over large parts of northern and central Europe and we can find them with new technologies as tine ash particles in the sediment deposits of lakes. Through counting of annual bands in these sediments we could precisely determine the age of this volcanic ash." Therefore, this ash material reflects a distinct time marker in the sediments of the lakes in the Eifel and in Norway.

Furthermore, lake sediments are very accurate climate archives, especially when they contain seasonal bands similar like tree rings. "It is a diligent piece of work to count and analyse thousands of these thin layers under the microscope to reconstruct climate year-by-year far back in time", illustrates Brauer.

The ash of the Katla volcanic eruption thus was deposited at the same time in the Eifel and in Norway. The sediments of the Eifel maar lake depict the rapid warming 100 years before the volcanic ash, while it is seen in the southern Norwegian lake sediment 20 years after the volcanic eruption. The same warming, but with a 120 difference in timing between the about 1200 km distant locations? Achim Brauer:

"We can explain this difference with the shift of hemispheric wind systems. Climate changed in both regions very rapid, but the polar front, that is the atmospheric boundary layer between cold polar air and the warmer air of the mid-latitudes, required more than 100 years to retreat from its glacial position at about the location of the Eifel at 50° N to its southern Norwegian position at 62° N."

Hence, the study provides evidence for a rapid change that slowly moved northwards. The result of this study has some implications on the understanding of both past and future climate change. The assumption of an everywhere and always synchronously changing climate must be questioned and climate models have to better consider such regional aspects.

*More information: C.S. Lane, A. Brauer, S.P.E. Blockley, P. Dulski: "Volcanic ash reveals a time-transgressive abrupt climate change during the Younger Dryas", Geology v. 41, no. 12, p. 1251 December 2013; DOI: 10.1130/G34867.1*

***http://nyti.ms/IYCHCU***

## Baffling 400,000-Year-Old Clue to Human Origins

***Scientists have found the oldest DNA evidence yet of humans' biological history. But instead of neatly clarifying human evolution, the finding is adding new mysteries.***

**By CARL ZIMMER**

In a paper in the journal Nature, scientists reported Wednesday that they had retrieved ancient human DNA from a fossil dating back about 400,000 years, shattering the previous record of 100,000 years.

The fossil, a thigh bone found in Spain, had previously seemed to many experts to belong to a forerunner of Neanderthals. But its DNA tells a very different story. It most closely resembles DNA from an enigmatic lineage of humans known as Denisovans. Until now, Denisovans were known only from DNA retrieved from 80,000-year-old remains in Siberia, 4,000 miles east of where the new DNA was found.

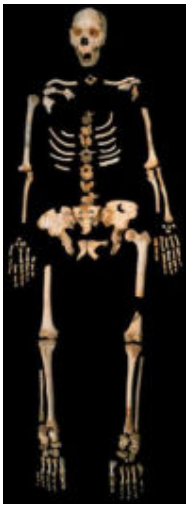
The mismatch between the anatomical and genetic evidence surprised the scientists, who are now rethinking human evolution over the past few hundred thousand years. It is possible, for example, that there are many extinct human populations that scientists have yet to discover. They might have interbred, swapping DNA. Scientists hope that further studies of extremely ancient human DNA will clarify the mystery.

"Right now, we've basically generated a big question mark," said Matthias Meyer, a geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and a co-author of the new study.

Hints at new hidden complexities in the human story came from a 400,000-year-old femur found in a cave in Spain called Sima de los Huesos ("the pit of bones" in Spanish). The scientific team used new methods to extract the ancient DNA from the fossil.

"This would not have been possible even a year ago," said Juan Luis Arsuaga, a paleoanthropologist at Universidad Complutense de Madrid and a co-author of the paper.

Finding such ancient human DNA was a major advance, said David Reich, a geneticist at Harvard Medical School who was not involved in the research. "That's an amazing, game-changing thing," he said.



Since the 1970s, Spanish scientists have brought out a wealth of fossils from the cave dating back hundreds of thousands of years. "The place is very special," said Dr. Arsuaga, who has found 28 nearly complete skeletons of humans during three decades of excavations.

Based on the anatomy of the fossils, Dr. Arsuaga has argued that they belonged to ancestors of Neanderthals, which lived in western Asia and Europe from about 200,000 to 30,000 years ago.

When Dr. Meyer and his colleagues drilled into the femur, they found ancient human DNA inside, just as they had hoped. "Our expectation was that it would be a very early Neanderthal," Dr. Meyer said.

But the DNA did not match that of Neanderthals. Dr. Meyer then compared it to the DNA of the Denisovans, the ancient human lineage that he and his colleagues had discovered in Siberia in 2010. He was shocked to find that it was similar. "Everybody had a hard time believing it at first," Dr. Meyer said. "So we generated more and more data to nail it down."

***The skeleton of a hominin recovered from Sima de los Huesos.*** **Javier Trueba, Madrid Scientific Films**

The extra research confirmed that the DNA belonged on the Denisovan branch of the human family tree.

The new finding is hard to reconcile with the picture of human evolution that has been emerging based on fossils and ancient DNA. Denisovans were believed to be limited to East Asia, and they were not thought to look so Neanderthal-like.

Based on previously discovered ancient DNA and fossil evidence, scientists generally agreed that humans' direct ancestors shared a common ancestor with Neanderthals and Denisovans that lived about half a million years ago in Africa.

Their shared ancestors split off from humans' lineage and left Africa, then split further into the Denisovans and Neanderthals about 300,000 years ago. The evidence suggested that Neanderthals headed west, toward Europe, and that the Denisovans moved east.

Humans' ancestors, meanwhile, stayed in Africa, giving rise to Homo sapiens about 200,000 years ago. Humans then expanded from Africa into Asia and Europe about 60,000 years ago. They then interbred not only with Neanderthals, but with Denisovans, too. Later, both the Denisovans and Neanderthals became extinct. "Now we have to rethink the whole story," Dr. Arsuaga said.

***An artist's interpretation of the hominins that lived near the Sima de los Huesos cave in Spain.*** **Javier Trueba, Madrid Scientific Films**

Dr. Arsuaga doubts that Denisovans were spread out across so much of the Old World, from Spain to Siberia, masquerading as Neanderthals. One alternative explanation is that the humans of Sima de los Huesos were not true Neanderthals, but belonged to the ancestors of both Denisovans and Neanderthals.

It is also possible that the newly discovered DNA was passed to both Neanderthals and Denisovans, but eventually disappeared from Neanderthals, replaced by other variants.

"It got lost in one lineage but made its way in the other," suggested Jean-Jacques Hublin, a Max Planck paleoanthropologist who was not involved in the research.

Beth Shapiro, an expert on ancient DNA at the University of California, Santa Cruz, favors an even more radical possibility: that the humans of Sima de los Huesos belong to yet another branch of humans. They might have been a species called Homo erectus, which originated about 1.8 million years ago and became extinct within the last few hundred thousand years. "The more we learn from the DNA extracted from these fossils, the more complicated the story becomes," Dr. Shapiro said.

This complicated story has come to light only because of advances over the past 20 years in retrieving ancient DNA. When an organism dies, its DNA breaks down into smaller and smaller fragments, while also becoming

contaminated with the DNA of other species like soil bacteria. So piecing the fossil DNA together is a bit like putting together a jigsaw puzzle created by a sadist.
In 1997, Svante Paabo of the Max Planck Institute and his colleagues, who had pioneered the techniques for retrieving DNA fragments, published a snippet of DNA from a Neanderthal fossil dating back about 40,000 years. They and other scientists then built on this success by searching for bits of DNA from other Neanderthals. In 2006, a team of French and Belgian researchers obtained a fragment of Neanderthal DNA dating back 100,000 years, which until now held the record for the oldest human DNA ever found.
Meanwhile, using improved methods, Dr. Paabo, Dr. Meyer and their colleagues assembled a rough draft of the entire Neanderthal genome in 2010.
That discovery shed light on how Neanderthals and humans' ancestors split from a common ancestor hundreds of thousands of years ago. It also revealed that Neanderthals and humans interbred about 50,000 years ago.
Around the same time as that discovery, Russian collaborators sent the Max Planck team 80,000-year-old fossils they had found in a cave in Siberia called Denisova. When the German scientists sequenced the entire genome from the finger bone of a girl, it turned out to be neither human nor Neanderthal, but from a separate lineage, which Dr. Paabo and his colleagues named Denisovans.
Dr. Meyer is hopeful that he and his colleagues will be able to get more DNA from the Spanish fossil, as well as other fossils from the site, to help solve the puzzle they have now stumbled across. "It's extremely hard to make sense of," Dr. Meyer said. "We still are a bit lost here."

***http://www.eurekalert.org/pub_releases/2013-12/uow-enj120413.php***

## Estrogen: Not just produced by the ovaries

***The brain can produce and release estrogen***

MADISON – A University of Wisconsin-Madison research team reports today that the brain can produce and release estrogen — a discovery that may lead to a better understanding of hormonal changes observed from before birth throughout the entire aging process. The new research shows that the hypothalamus can directly control reproductive function in rhesus monkeys and very likely performs the same action in women.
Scientists have known for about 80 years that the hypothalamus, a region in the brain, is involved in regulating the menstrual cycle and reproduction. Within the past 40 years, they predicted the presence of neural estrogens, but they did not know whether the brain could actually make and release estrogen.
Most estrogens, such as estradiol, a primary hormone that controls the menstrual cycle, are produced in the ovaries. Estradiol circulates throughout the body, including the brain and pituitary gland, and influences reproduction, body weight, and learning and memory. As a result, many normal functions are compromised when the ovaries are removed or lose their function after menopause.
"Discovering that the hypothalamus can rapidly produce large amounts of estradiol and participate in control of gonadotropin-releasing hormone neurons surprised us," says Ei Terasawa, professor of pediatrics at the UW School of Medicine and Public Health and senior scientist at the Wisconsin National Primate Research Center. "These findings not only shift the concept of how reproductive function and behavior is regulated but have real implications for understanding and treating a number of diseases and disorders."
For diseases that may be linked to estrogen imbalances, such as Alzheimer's disease, stroke, depression, experimental autoimmune encephalomyelitis and other autoimmune disorders, the hypothalamus may become a novel area for drug targeting, Terasawa says. "Results such as these can point us in new research directions and find new diagnostic tools and treatments for neuroendocrine diseases."
The study, published today in the Journal of Neuroscience, "opens up entirely new avenues of research into human reproduction and development, as well as the role of estrogen action as our bodies age," reports the first author of the paper, Brian Kenealy, who earned his Ph.D. this summer in the Endocrinology and Reproductive Physiology Program at UW-Madison. Kenealy performed three studies. In the first experiment, a brief infusion of estradiol benzoate administered into the hypothalamus of rhesus monkeys that had surgery to remove their ovaries rapidly stimulated GnRH release. The brain took over and began rapidly releasing this estrogen in large pulsing surges.
In the second experiment, mild electrical stimulation of the hypothalamus caused the release of both estrogen and GnRH (thus mimicking how estrogen could induce a neurotransmitter-like action). Third, the research team infused letrazole, an aromatase inhibitor that blocks the synthesis of estrogen, resulting in a lack of estrogen as well as GnRH release from the brain. Together, these methods demonstrated how local synthesis of estrogen in the brain is important in regulating reproductive function.
The reproductive, neurological and immune systems of rhesus macaques have proven to be excellent biomedical models for humans over several decades, says Terasawa, who focuses on the neural and endocrine

mechanisms that control the initiation of puberty. "This work is further proof that these animals can teach us about so many basic functions we don't fully understand in humans."
Leading up to this discovery, Terasawa said, recent evidence had shown that estrogen acting as a neurotransmitter in the brain rapidly induced sexual behavior in quails and rats. Kenealy's work is the first evidence of this local hypothalamic action in primates, and in those that don't even have ovaries.
"The discovery that the primate brain can make estrogen is key to a better understanding of hormonal changes observed during every phase of development, from prenatal to puberty, and throughout adulthood, including aging," Kenealy says.

***http://www.eurekalert.org/pub_releases/2013-12/bidm-sft120413.php***

## Study finds that carbon monoxide can help shrink tumors and amplify effectiveness of chemotherapy

***Therapeutic benefits appear linked to cell's energy status; used in combination with chemo, CO helps spare healthy tissue***

BOSTON -- In recent years, research has suggested that carbon monoxide, the highly toxic gas emitted from auto exhausts and faulty heating systems, can be used to treat certain inflammatory medical conditions. Now a study led by a research team at Beth Israel Deaconess Medical Center (BIDMC) shows for the first time that carbon monoxide may also have a role to play in treating cancer.
The surprising new findings, described in the December issue of the journal Cancer Research, show that in cell culture and animal models carbon monoxide (CO) can both prevent tumor growth in prostate and lung cancers and can amplify the effectiveness of chemotherapy 1,000-fold – while sparing noncancerous tissue from chemo's sometimes debilitating side effects.
"We found that in small, carefully controlled doses, CO not only mimicked the effects of chemotherapy agents by blocking proliferation of cancer cells, but also amplified the toxic effects of the chemotherapy drugs doxorubicin and camptothecin to accelerate cancer cell death," says senior author Leo Otterbein, PhD, an investigator in the Transplant Institute in BIDMC's Department of Surgery and Associate Professor of Surgery at Harvard Medical School. "Importantly and rather unique is that CO also helped to protect normal tissue from chemotherapy, which is an unfortunate side effect of the treatments."
The new discovery appears to hinge on CO's ability to switch the metabolic state of cancer cells so that tumors essentially work themselves to death. "There are fundamental differences in the metabolism of normal cells and cancer cells," explains Otterbein. "Cancer cells are able to alter their metabolism in processing sugars and other energy sources, which enable them to rapidly proliferate and spread. This shift in metabolism is known as the Warburg Effect. Our findings indicate that CO essentially induces an 'anti-Warburg' effect, rapidly fueling cancer cell bioenergetics by compelling the cancer cell to increase respiration, which ultimately results in metabolic exhaustion."
The body naturally generates CO under stress through the increased expression of the gene heme oxygenase-1 (HO-1 Hmox1), a cytoprotective stress response gene that generates CO as it catabolizes heme, an essential component of many proteins such as hemoglobin. The increase in HO-1 has been shown to occur under numerous and diverse stressors, such as inflammation, trauma and even tissue repair. Tumors, however, are often absent this capability because HO has become inactive and unable to generate sufficient levels of CO. In this new paper, Otterbein and first author Barbara Wegiel, PhD, also an investigator in BIDMC's Transplant Institute, wanted to find out if a tumor's inability to produce CO naturally was what was fueling cancer growth.
"If A plus B equals C, then, we reasoned, if you administered carbon monoxide to tumors, you would reestablish a tumor cell's ability to regulate its cell growth, and so, too, slow that growth," says Otterbein.
The authors first conducted a detailed analysis of more than 500 tumor samples from prostate cancer patients.
"Through these biopsies, we confirmed expression of HO-1," explains Wegiel, who is also an Assistant Professor of Surgery at HMS. "But we found that HO-1 in the tumor was simply not active. It was not producing sufficient amounts of CO, and we thought this was contributing to altered cell growth and malignancy."
This finding led to their hypothesis that HO-1, through its ability to generate CO, was regulating the growth of cancer cells, a discovery that had been observed and well described in other cell types. To test this hypothesis, mice with established tumors were started on a regimen of inhaled CO of one hour per day at a safe, low concentration, equal to that approved for use in humans in ongoing clinical trials. Tumor size was measured daily over four to six weeks. In the cancer cell CULTURES, metabolic activity in the mitochondria – the cells' energy-generating organelle-- were measured using biochemical markers as well as imaging techniques.

"We found that exposure to CO sensitized the prostate cancer cells -- but not the normal cells -- to chemotherapy," explains Otterbein. "CO targeted mitochondria activity in cancer cells as evidenced by higher oxygen consumption, free radical generation and, ultimately, mitochondrial collapse.
"Collectively, our findings indicated that CO induces an anti-Warburg effect by rapidly fueling cancer cell bioenergetics, ultimately resulting in metabolic exhaustion," he adds. Importantly, CO protected normal cells from DNA damage generated by cytotoxic agents, in part by reducing oxygen consumption and eliciting a hibernation-like state in these cells. "Essentially, these normal cells entered growth arrest and slowed their metabolic rate, in marked contrast to the cancer cells, which continued to consume oxygen at a rate that ultimately led to their demise."
While the authors note that more researc h will be needed to confirm these findings, they provide a promising new direction for cancer treatment.
"Chemotherapy remains the first-line therapy for many types of cancer, including breast and lung cancers," notes study coauthor and BIDMC Chief Academic Officer Vikas Sukhatme, MD, PhD. "But chemotherapy's debilitating side effects and limited effectiveness are well known. This new finding opens up the possibility of new therapeutic interventions that take advantage of powerful chemotherapy drugs, perhaps making them even more potent while simultaneously limiting their terrible side effects and damage to normal cells and tissues. There are ongoing innovative methodologies being designed and tested to deliver CO directly to the tumor site, which might obviate the need for additional drugs. Indeed, small molecules are being designed that can carry CO as a cargo and deliver it in a tissue-specific manner."
*This work was supported by grants from the National Institutes of Health (HL-071797; HL-076167, as well as support from AHA, the Julie Henry Fund, the British Heart Foundation and Medical Research Council.*
*In addition to Otterbein, Wegiel and Sukhatme, study coauthors include BIDMC investigators David Gallo, Eva Csizmadia, Clair Harris, Pankaj Seth and Pier Paolo Pandolfi and investigators John Belcher, Gregory Vercellotti, Leszek Helczynski, Anders Bjartell, Jenny Liao Persson, Nuno Penacho and Asif Ahmed.*

***http://bit.ly/1d224MC***

## Dangerous Global Warming Closer Than You Think, Climate Scientists Say

***Two new reports lay out the case for fast action and increased awareness***

**By David Biello | Wednesday, December 4, 2013 | 102**

Abrupt climate change is not only imminent, it's already here. The rapid dwindling of summer Arctic sea ice has outpaced all scientific projections, which will have impacts on everything from atmospheric circulation to global shipping. And plants, animals and other species are already struggling to keep up with rapid climate shifts, increasing the risk of mass extinction that would rival the end of the dinosaurs. So warns a new report from the U.S. National Research Council.
That's exactly why longtime climate scientist James Hansen and a panoply of scientists and economists are urging in another new paper that current efforts to restrain global warming are woefully inadequate. In particular, global negotiations to limit global warming to no more than 2 degrees Celsius risk "wrecking the planet," in the words of lead author Hansen, recently retired head of the Goddard Institute for Space Studies and a researcher at Columbia University's Earth Institute.
"We started this paper to provide a basis for legal actions against governments for not doing their jobs and protecting the rights of young people and future generations," Hansen said of the paper, entitled "Assessing 'Dangerous Climate Change.'" "We can't burn all these fossil fuels. There is no recognition of this in government policies."
The paper, published in PLOS ONE, lays out the case for why fossil fuel emissions to date are dangerous enough to permanently alter the planet's climate—raising $CO_2$ concentrations in the atmosphere above 400 parts-per-million, or levels not seen in at least 3 million years. Global emissions of $CO_2$ from burning fossil fuels—which set another new high in 2012, according to the Global Carbon Project—must decline to zero new pollution within the next few decades, according to the analysis. "Affordable, clean energy is probably the biggest requirement that the planet has," Hansen noted at a gathering of journalists at Columbia University to discuss the new analysis.
Given the size of the problem—the fossil fuels of coal, oil and natural gas still provide more than 80 percent of the world's energy—an "all of the above" clean energy effort will be required, according to Hansen and his co-authors. That includes geothermal, hydropower, nuclear, solar, wind and further development of technologies to capture $CO_2$ from fossil fuel burning and permanently store it in some way. Increasing efficiency in the use of such energy as well as switching cars from running on gasoline to electricity will also be vital. "What's called normal is completely reckless," said co-author and economist Jeffrey Sachs of the Earth Institute, addressing the growth rates in fossil fuel pollution of roughly 3 percent per year, putting the world on a pathway to roughly

4 degrees C of warming by century's end. "To decarbonize the energy system very deeply would require a scale of effort unlike anything seen almost anywhere in the world."
In fact, by the paper's math, emissions must start to fall by 6 percent per year globally starting now, falling below 350 ppm as soon as possible. Delay increases the need as well as making the return to 350 ppm even harder. To date, the fastest decarbonizations—such as France's switch to nuclear for electricity generation or Denmark's drive for wind power—have managed a top speed of roughly 2 percent a year, and in relatively small countries. That rate would have been fine if it had begun worldwide in 1995 but something much faster is now required, according to the analysis.
The key to accelerating that change may be a tax or other fee on carbon that would force fossil fuels to pay the full costs of their environmental impacts. Even at a price as high as $40 per metric ton that would impose a cost of just 1 percent of global economic output, Sachs notes. Already, the U.S. government has instituted a societal cost of continuing CO2 pollution—assumed now to be $35 per ton—in its economic modeling for cost-benefit analyses of various policies.
But the most necessary policy may be a plan for how to achieve such reductions, including measures to pay for it, whether a carbon tax or some kind of clean energy bond to be paid off in future. "At low cost it is possible to avoid devastating risks," Sachs argued. "This is a winnable proposition. It's got the makings of a success story but it's hard."
Starting that now is more important than ever. Already, the world has warmed by 0.8 degree C over the course of the 20th century. "It's true that we're going to pass 500 gigatonnes of carbon and one degree" of warming, Hansen said. "But that doesn't mean we have to pass the two degree threshold."
There is good news. Scientific study suggests that threats like a shift in ocean currents or a rapid meltdown of Arctic permafrost and frozen methane in the oceans is unlikely to happen abruptly. "There is enough carbon in the permafrost and oceans to equal all the coal, oil and gas and there's no reason to think it won't come out as the climate warms up," explained climatologist Jim White of the University of Colorado–Boulder, chairman of the NRC study examining the relative risks of rapid climate change, during a press conference presenting the study. But "it will not come out abruptly," he said, adding that in the meantime, "we still have to adapt to all that carbon coming out if we don't keep the temperature down."
Surprises are inevitable—perhaps best summarized by old mapmakers in the phrase "here be dragons" for areas of the unknown—especially given the paucity of monitoring some of the biggest threats. Relatively few measurements of methane in the Arctic are taken, nor is there any oversight of the ongoing meltdown of the West Antarctic Ice Sheet as warmer waters lap at its base. "We don't do that," White noted. "There are areas of observations where we are largely blind but we know we should be watching."
The report calls for an Abrupt Change Early Warning System, potentially gathering together the monitoring and modeling efforts of an array of federal agencies—National Oceanic and Atmospheric Administration, National Aeronautics and Space Administration, the National Science Foundation, and U.S. Geological Survey, for example—and then feeding that physical scientific information into social science efforts to enhance warnings, much like the "cone of uncertainty" now used in hurricane warnings. After all, just 12,000 years ago the Earth's climate seems to have warmed by several degrees C—bringing to an end an episode of colder average temperatures known as the Younger Dryas—in a matter of decades.
The reality is, however, that the U.S. is further cutting back on such efforts, including cuts to NOAA's greenhouse gas monitoring network, delayed satellite launches for both civilian and military weather observations and other monitoring systems. "As a scientist, I like to think we study the planet well enough that we're not going to be blindsided," White said. "As a realist, I'm pretty sure we're going to be blindsided."
Plus, as recent United Nations negotiations in Warsaw proved yet again, the international argument on climate change is about who is responsible rather than what needs to be done. Surprises like the rapid meltdown of Arctic sea ice are therefore inevitable, but extreme global warming still isn't, necessarily. "It's not tipping points I worry about but points of no return," Hansen said. "It's not whether things happen quickly but that they're guaranteed."

***http://www.livescience.com/41680-how-moho-forms-earths-crust.html***

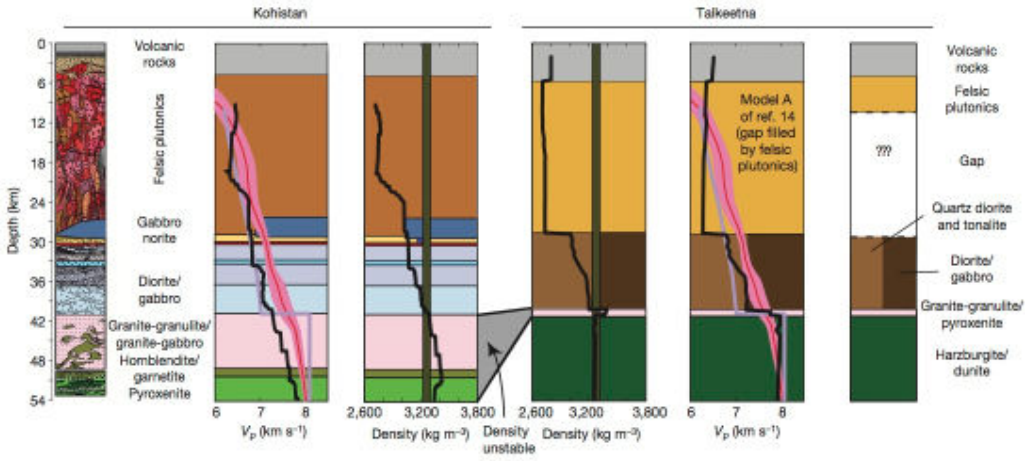
## How a Mysterious 'Moho' Forms Beneath Earth's Crust

***A dense crystalline "rain" falling into Earth's mantle could explain how a mysterious seismic boundary forms beneath the crust***

**By Becky Oskin, Staff Writer | December 04, 2013 01:00pm ET**

A dense crystalline "rain" falling into Earth's mantle could explain how a mysterious seismic boundary forms beneath the crust, according to a study published today (Dec. 4) in the journal Nature. The model, based on rock evidence from volcanic islands that smashed into Asia and Alaska, confirms long-standing ideas about

how continents are born. "There are a lot of things I think this study will resolve and a lot of questions that will remain," said lead author and MIT geologist Oliver Jagoutz.
The seismic boundary investigated by Jagoutz and co-author Mark Behn, of the Woods Hole Oceanographic Institution in Woods Hole, Mass., is called the Moho, after Croatian seismologist Andrija Mohorovicic. In 1909, Mohorovicic realized earthquake waves suddenly sped up at a sharply defined boundary that hovers about 25 miles (40 kilometers) beneath continents. The discovery revealed Earth was divided, with a lighter crust and denser mantle where the seismic waves traveled faster.
Because the Moho is so deep, no one has ever seen it directly, but scientists have spent entire careers explaining why it exists and how it forms.




***A schematic illustration of the properties of rocks from Pakistan and Alaska used to develop a new model for how the Moho forms.*** **Nature**

**Misplaced Moho**

One enduring puzzle has been the missing Moho — the boundary's absence beneath volcanic island chains, such as Japan's Izu-Bonin islands, that rise above colliding tectonic plates. Because these "island arcs" are the building blocks of continents, the missing Moho is a mystery. For example, the East Coast of North America has a clear, crisp Moho, but it is also quilted from scores of volcanic chains slamming into the continent's edge several hundred million years ago. Another problem is the rocks in continents are about 10 percent richer in silica than oceanic crust, which is the source of magma that feeds volcanic island chains.
"If we want to produce continental crust in arcs, we are left with two problems," Jagoutz told LiveScience's OurAmazingPlanet. "The rocks we find on the surface of continents all resemble lavas that are erupted in subduction zones, but there needs to be a mechanism that brings the melt from 50 to 60 percent [richer in silica]," he said. "Another problem we have is the structural problem. Somehow we need to introduce this major structural discontinuity, the Moho, that we don't have in arcs but we have in continents."
To solve the Moho mystery, Jagoutz and Behn found a way to look at the lower crust via fragments of former volcanic island chains now shoved up to the surface in mountain belts in Pakistan and Alaska. These rocks were once 25 to 31 miles (40 to 50 km) deep. They created a geophysical model of the crust based on the rocks, and compared it to seismic data from today's island arcs.

**Planetary windows**

The Pakistan rocks resemble modern island arc settings. There's no sharp density contrast that would produce a Moho boundary. The layers reveal a thick, continuous section of rocks of similar density, such as gabbros, at the depth of the Moho. But in Alaska, these rocks are missing. Instead, at the depth where the Moho would sit, there's a sharp density increase in the rock layers, with rocks called harzburgites and dunites instead of gabbros. Jagoutz thinks the missing dense rocks provide the clue to what happens at volcanic arcs.
Inside the Earth, in the lower crust, a "rain" of dense crystalline material (called cumulates) falls from the base of the crust. The rocks are denser than the underlying mantle and sink down into the Earth. This process, known as delamination or foundering, continually peels off pieces of the lower crust.
"It's like icebergs, but the stuff that's actually dropping off is actually underwater," Jagoutz said.
Removing these dense rock leaves lighter, silica-rich materials behind — like the rocks found in continents, Jagoutz said.

**Sinking down**

The researchers think the Moho starts to appear with big changes in volcanism, such as when melting stops or subduction shuts off. Because volcanic island chains appear above subduction zones, where a tectonic plate sinks into the mantle and releases fluids that trigger melting, new magma will rise upwards and replace the missing crust. But without new magma replenishing the crystalline rain, eventually a sharp boundary will appear between lighter material in the crust and the dense mantle below.

"When this happens, the mantle will remain relatively hot for a while and the material will continue to sink back down," Jagoutz said.
Geologist Suzanne Kay of Cornell University, one of the original proponents of crustal delamination in island arcs, said the study was "an interesting paper" but doesn't cover significant new ground.
"The idea of delamination in oceanic and continental arcs and the link with the composition of the continental crust by delamination have been around for more than 20 years, and others are also thinking of the ultimate fate of the delaminated material," Kay said in an email interview.

***http://www.medscape.com/viewarticle/815378?src=rss***

## Excitement Mounting That Radiation Will Eliminate HIV

***Radioimmunotherapy in conjunction with antiretroviral triple therapy can effectively kill HIV-infected cells from patients, a new study has shown.***

**Lara C. Pullen, PhD**

CHICAGO - "The cells are being steadily killed by a dose of radiation," explained Ekaterina Dadachova, PhD, professor of radiology, microbiology, and immunology at the Albert Einstein College of Medicine in the Bronx, New York. Dr. Dadachova presented the research to an excited audience here at the Radiological Society of North America 99th Scientific Assembly and Annual Meeting. She began her talk by reminding the audience that the conference started on December 1, World AIDS Day.
The safety of radioimmunotherapy is well established in the field of oncology, where tumor cell burdens are approximately 1000 times greater than those seen in HIV patients being treated with triple therapy. This makes HIV a comparatively light load for radioimmunotherapy, according to those most familiar with the technique.
Current treatment options for HIV include antiretrovirals, which can dramatically increase a patient's lifespan and has transformed HIV from an acute disease. "HIV is now a chronic disease, but people are still dying from it and there is still no cure," Dr. Dadachova said.
Medications suppress viral reproduction, but they do not kill infected cells. Antiretrovirals also have a host of problems, including high cost, toxicity, nonadherence, and drug resistance.
Most important, viremia returns after treatment cessation. This is because both cellular and anatomic reservoirs of HIV in the body maintain the infection.
At the cellular level, even with antiretrovirals, the patient's body contains long-lived cell populations that are infected with HIV and are capable of surviving for prolonged periods of time. Resting CD4+ T-cells, macrophages, dendritic cells, and hematopoietic cells can all serve as reservoirs for HIV.
Anatomically, HIV also persists in the brain, and this has traditionally been a very difficult area for HIV therapeutics to access. The world needs a strategy for eradicating HIV, said Dr. Dadachova. She then proceeded to describe her team's strategy using radioimmunotherapy.
The approach is effective against HIV-infected cells because it binds to a specific antigen and kills the cells. To be successful as a therapy, it requires an antigen target that in no way resembles a human antigen. If such an antigen can be found, then "1 or 2 hits per cell is enough to destroy the cell," explained Dr. Dadachova.
Her team used the HIV antigen gp41 to generate the 2556 antibody that binds specifically to HIV-infected cells. Radiolabeled human antibody binds to the viral gp41 protein expressed on the surface of the HIV-infected lymphocyte and the cell is killed with alpha radiation.
The researchers previously used gp41 radioimmunotherapy in mice with severe combined immunodeficiency that were injected with infected human cells (PLoS One. 2012;7:e31866). "We are basically able to eliminate the HIV-infected cells in those mice," Dr. Dadachova said enthusiastically. More important, they were able to eliminate HIV-infected cells in the brains of the mice.
Although the team's success with mice was exciting, she noted that they still did not know whether radioimmunotherapy would work in patients being treated with antiretroviral therapy. No one could say what the interaction between radioimmunotherapy, HIV, and antiretrovirals would look like. Would the suppressed viral replication also suppress the expression of gp41 below the level needed for radioimmunotherapy?
"That's where the Bill and Melinda Gates Foundation came in," she said. "They funded our study."
This year, Dr. Dadachova and her team performed an ex vivo study on clinical samples. They found that radioimmunotherapy killed the infected patient's lymphocytes over a full range of doses.
They also used an in vitro model to demonstrate that the radiolabeled antibody crosses the blood–brain barrier without disturbing the tight junctions of the cells.
"It has fantastic potential," said Gary Whitman, MD, professor of radiology at the University of Texas M.D. Anderson Cancer Center in Houston. Dr. Dadachova will next be partnering with physicians in South Africa to enroll patients there in the first radioimmunotherapy clinical trial. She said she expects the first results by the

end of 2014. She also reported that she is applying to the National Institutes of Health for funding to continue the research in the United States.
The treatment regimen will likely consist of a single injection of radioimmunotherapy, she explained. Because bismuth-213 is a very short-lived isotope, all radioactivity will be gone from the patient in 4 hours. Follow-up testing will reveal whether the patient rebounds and requires another treatment.
Many in the room said the precedence of radioimmunotherapy in the treatment of cancer fuels their hope that people will truly have something to celebrate next World AIDS Day.
*Dr. Dadachova and Dr. Whitman have disclosed no relevant financial relationships.*

***http://phys.org/news/2013-12-scientists-vast-undersea-freshwater-reserves.html***

## Scientists discover vast undersea freshwater reserves

***Australian researchers say they have identified vast reserves of fresh water trapped beneath the ocean floor off Australia, China, North American and South America***

Australian researchers said Thursday they had established the existence of vast freshwater reserves trapped beneath the ocean floor which could sustain future generations as current sources dwindle.
Lead author Vincent Post, from Australia's Flinders University, said that an estimated 500,000 cubic kilometres (120,000 cubic miles) of low-salinity water had been found buried beneath the seabed on continental shelves off Australia, China, North America and South Africa.
"The volume of this water resource is a hundred times greater than the amount we've extracted from the Earth's sub-surface in the past century since 1900," said Post of the study, published in the latest edition of Nature.
"Freshwater on our planet is increasingly under stress and strain so the discovery of significant new stores off the coast is very exciting. "It means that more options can be considered to help reduce the impact of droughts and continental water shortages."
UN Water, the United Nations' water agency, estimates that water use has been growing at more than twice the rate of population in the last century due to demands such as irrigated agriculture and meat production.
More than 40 percent of the world's population already live in conditions of water scarcity. By 2030, UN Water estimates that 47 percent of people will exist under high water stress. Post said his team's findings were drawn from a review of seafloor water studies done for scientific or oil and gas exploration purposes.
"By combining all this information we've demonstrated that the freshwater below the seafloor is a common finding, and not some anomaly that only occurs under very special circumstances," he told AFP.
The deposits were formed over hundreds of thousands of years in the past, when the sea level was much lower and areas now under the ocean were exposed to rainfall which was absorbed into the underlying water table. When the polar icecaps started melting about 20,000 years ago these coastlines disappeared under water, but their aquifers remain intact—protected by layers of clay and sediment.
Post said the deposits were comparable with the bore basins currently relied upon by much of the world for drinking water and would cost much less than seawater to desalinate. Drilling for the water would be expensive, and Post said great care would have to be taken not to contaminate the aquifers. He warned that they were a precious resource. "We should use them carefully: once gone, they won't be replenished until the sea level drops again, which is not likely to happen for a very long time," Post said.
*More information: "Offshore fresh groundwater reserves as a global phenomenon" by Vincent E.A. Post, Jacobus Groen, Henk Kooi, Mark Person, Shemin Ge and W. Mike Edmunds: www.nature.com/nature/journal/v504/n7478/full/nature12858.html*

***http://www.eurekalert.org/pub_releases/2013-12/cp-ebs112713.php***

## Electrical brain stimulation may evoke a person's 'will to persevere'

***What gives some people the ability to persevere through difficult situations that others may find insurmountable?***

The answer is no doubt a complicated one that may be beyond our full understanding, but new research publishing online December 5 in the Cell Press journal Neuron provides some intriguing insights. The study pinpoints a region of the brain that, when stimulated, causes an individual to anticipate a challenge and possess a strong motivation to overcome it.
"That few electrical pulses delivered to a population of brain cells in conscious human individuals give rise to such a high level set of emotions and thoughts we associate with a human virtue such as perseverance tells us that our unique human qualities are anchored dearly in the operation of our brain cells," says lead author Dr. Josef Parvizi, of the Department of Neurology and Neurological Sciences at Stanford University.
The study conducted by Dr. Parvizi and his team involved two individuals with epilepsy who had electrodes implanted in their brains to help doctors learn about the source of their seizures. The electrodes were situated in the anterior midcingulate cortex, a brain region that is thought to be involved in emotions, pain, and decision making.

When electrical charge was delivered to a location within this region, both patients described feeling the expectation of an imminent challenge coupled with a determined attitude to surmount it. This was accompanied by increased heart rate and physical sensations in the chest and neck. They did not experience any of these psychological or physical effects when they thought that their brains were being stimulated but no electrical charge was delivered. The same effects did not occur with stimulation of nearby regions only 5 mm away.
Imaging experiments conducted in Dr. Michael Greicius' laboratory at Stanford revealed that the site of stimulation in both patients was at the core of a network linking the anterior midcingulate cortex to other regions of the brain. "Our study pinpoints the precise anatomical coordinates of neuronal populations, and their associated network, that support complex psychological and behavioral states associated with perseverance," explains Dr. Parvizi.
The findings suggest that differences in the structure and function of this network may be linked with innate differences in our abilities to cope during tough situations. The results may even pertain to psychopathological conditions in which people experience a significantly reduced capacity to endure psychological or physical distress.
"These innate differences might potentially be identified in childhood and be modified by behavioral therapy, medication, or, as suggested here, electrical stimulation," says Dr. Parvizi.
*Neuron, Parvizi et al.: "The Will to Persevere Induced by Electrical Stimulation of the Human Anterior Cingulate Cortex."*

***http://www.eurekalert.org/pub_releases/2013-12/uoaf-uru120513.php***

## UAlberta researchers uncover why combination drug treatment ineffective in cancer clinical trials

***1 drug prevented the other drug from working***

Medical researchers at the University of Alberta have discovered that combination drug therapy didn't work well in clinical trials for cancer patients because one drug was making the other drug ineffective.
Faculty of Medicine & Dentistry researcher Michael Sawyer and his colleagues, including first author Vijaya Damaraju, recently published their findings in the peer-reviewed journal, Clinical Cancer Research.
In the '80s and '90s, cancer research focused on finding out which proteins "drove" cancers. New drugs targeting these proteins worked well by themselves, and some in the field believed combining the new drugs with the older chemotherapy drugs would work better than either drug by itself.
"So the pharmaceutical industry developed a combination of drugs in which we thought we were giving two drugs at once, but in actual fact the one drug we were giving was completely blocking the actions of the other drug," said Sawyer, who works in the Faculty's Department of Oncology.
"The old chemotherapy drugs required special proteins to get inside of cells to work. What our team discovered is that the new chemotherapy drugs prevented these proteins from carrying the old chemotherapy drugs into the cell. No one was able to figure out why this combination of drugs didn't work, but now we have discovered what went wrong." Sawyer says the findings will guide oncologists about how cancer drugs should be combined, or whether certain drugs should be combined at all.
"This will save us from doing millions of dollars in clinical trials that have no chance of working out. These findings show oncologists we have to be careful about which drugs should be combined. You have to think about how they actually work, especially in ways which no one understood before.
"Our research was actually like peeling an onion. Once we figured out the answer to one question, then other things the drugs did make more sense. Ultimately, the findings mean we'll be able to design better combination drug therapies. We'll know which drugs to combine, and when and how drugs can be combined. This will require more precise scheduling and dosing than what we've done to date."
He stressed the only patients impacted were those in clinical trials – the combination drug therapy had not yet become common clinical practice because it wasn't working the way oncologists had hoped. And for those patients who took part in the clinical trials, the one chemotherapy drug was still very effective – so those patients still received excellent care and drugs that properly targeted their cancers.
Sawyer and his team are continuing their research in this area. Their research was funded by the former Alberta Cancer Board, the Alberta Cancer Foundation and Alberta Innovates – Health Solutions.

***http://www.eurekalert.org/pub_releases/2013-12/nrr-wit120513.php***

## What is the central analgesic mechanism of acupuncture for migraine?

***The central analgesic mechanism of acupuncture for migraine remains poorly understood.***

Acupuncture has been shown to become a recommended treatment for migraine sufferers. However, a single acupuncture stimulus cannot be indicative of the cumulative effects of acupuncture treatment. Prof. Fanrong Liang and colleagues from Chengdu University of Traditional Chinese Medicine recruited migraine sufferers

receiving 1 month of acupuncture treatment and explored the central analgesic mechanism of the cumulative effects of acupuncture for migraine. The aim of their study was to examine changes in brain functional activity and central networks in subjects with migraine undergoing acupuncture at Shaoyang uncommon acupoints. This trial has been registered on http://www.clinicaltrial.gov and provides a further explanation of the central analgesic mechanism by which acupuncture at Shaoyang acupoints treats migraine. These findings are published in the Neural Regeneration Research (Vol. 8, No. 28, 2013).

*Article: " A central analgesic mechanism of acupuncture for migraine," by Lei Lan1, Yujie Gao2, Fang Zeng1, Wei Qin3, Mingkai Dong1, Mailan Liu1, Taipin Guo1, Fanrong Liang1 (1 School of Acupuncture and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, Sichuan Province, China; 2 School of Traditional Chinese Medicine, Ningxia Medical University, Yinchuan 750004, Ningxia Hui Autonomous Region, China; 3 Life Science Research Center, School of Life Sciences and Technology, Xidian University, Xi'an 710071, Shaanxi Province, China)*

*Lan L, Gao YJ, Zeng F, Qin W, Dong MK, Liu ML, Guo TP, Liang FR. A central analgesic mechanism of acupuncture for migraine: an ongoing functional MRI study. Neural Regen Res. 2013;8(28):2649-2655.*

***http://www.eurekalert.org/pub_releases/2013-12/nrr-pam120513.php***

## Pre-moxibustion and moxibustion prevent Alzheimer's disease

***An increasing number of clinical and animal studies have confirmed that acupuncture is effective for the treatment of Alzheimer's disease.***

Moxibustion is reported to be more effective than electro-acupuncture for improving space-recognizing memory ability in aged mice, suggesting that moxibustion is another alternative or complementary therapy used to treat Alzheimer's disease. Dr. Yanjun Du and team from Hubei University of Chinese Medicine, China only used suspended moxibustion (also named warming moxibustion, scarring moxibustion, or herb-partition moxibustion) on Baihui (GV20) and Shenshu (BL23) acupoints to observe the action of pre-moxibustion on preventing apoptosis in a rat model of Alzheimer's disease. The pre-moxibustion group was treated with moxibustion for eight courses (each course lasting for 6 days) prior to the exposure and 14 days after Aβ1–42 exposure. Results showed no evidence of apoptosis in hippocampal neurons, a significantly reduced apoptosis rate of neurons and improved learning and memory abilities were observed in the Alzheimer's disease model. In particular, moxibustion prior to Aβ1–42 exposure was more effective than moxibustion after Aβ1–42 exposure in protecting the neuronal structure and lowering the apoptosis rate. Their findings, published in the Neural Regeneration Research (Vol. 8, No. 30, 2013), indicate that a combination of preventive and therapeutic moxibustion has a beneficial effect for the prevention of Alzheimer's disease development.

*Article: " Pre-moxibustion and moxibustion prevent Alzheimer's disease," by Yanjun Du1, Ruolan Liu2, Guojie Sun1, Peiyan Meng1, Jie Song1 (1 College of Acupuncture and Moxibustion, Hubei University of Chinese Medicine, Wuhan 430061, Hubei Province, China; 2 Department of Rehabilitation, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei Province, China)*

*Du YJ, Liu RL, Sun GJ, Meng PY, Song J. Pre-moxibustion and moxibustion prevent Alzheimer's disease. Neural Regen Res. 2013;8(30):2811-2819.*

***http://www.eurekalert.org/pub_releases/2013-12/afot-cob120513.php***

## Coffee or beer? The choice could affect your genome

***Tel Aviv University says caffeine and alcohol can change a part of DNA linked to aging and cancer***

Coffee and beer are polar opposites in the beverage world. Coffee picks you up, and beer winds you down. Now Prof. Martin Kupiec and his team at Tel Aviv University's Department of Molecular Microbiology and Biotechnology have discovered that the beverages may also have opposite effects on your genome. Working with a kind of yeast that shares many important genetic similarities with humans, the researchers found that caffeine shortens and alcohol lengthens telomeres – the end points of chromosomal DNA, implicated in aging and cancer.

"For the first time we've identified a few environmental factors that alter telomere length, and we've shown how they do it," said Prof. Kupiec. "What we learned may one day contribute to the prevention and treatment of human diseases." Researchers from TAU's Blavatnik School of Computer Science and Columbia University's Department of Biological Sciences collaborated on the research, published in PLOS Genetics.

**Between death and immortality**

Telomeres, made of DNA and proteins, mark the ends of the strands of DNA in our chromosomes. They are essential to ensuring that the DNA strands are repaired and copied correctly. Every time a cell duplicates, the chromosomes are copied into the new cell with slightly shorter telomeres. Eventually, the telomeres become too short, and the cell dies. Only fetal and cancer cells have mechanisms to avoid this fate; they go on reproducing forever.

The researchers set out to expand on a 2004 study by Nobel Prize-winning molecular biologist Prof. Elizabeth Blackburn, which suggested that emotional stress causes the shortening of the telomeres characteristic of aging,

presumably by generating free radicals in the cells. The researchers grew yeast cells in conditions that generate free radicals to test the effect on telomere length. They were surprised to find that the length did not change. They went on to expose the yeast cells to 12 other environmental stressors. Most of the stressors – from temperature and pH changes to various drugs and chemicals – had no effect on telomere length. But a low concentration of caffeine, similar to the amount found in a shot of espresso, shortened telomeres, and exposure to a 5-to-7 percent ethanol solution lengthened telomeres.

**From yeasts to you**

To understand these changes, the TAU researchers scanned 6,000 strains of the yeast, each with a different gene deactivated. They then conducted genetic tests on the strains with the longest and shortest telomeres, revealing that two genes, Rap1 and Rif1, are the main players mediating environmental stressors and telomere length. In total, some 400 genes interact to maintain telomere length, the TAU researchers note, underscoring the importance of this gene network in maintaining the stability of the genome. Strikingly, most of these yeast genes are also present in the human genome.

"This is the first time anyone has analyzed a complex system in which all of the genes affecting it are known," said Prof. Kupiec. "It turns out that telomere length is something that's very exact, which suggests that precision is critical and should be protected from environmental effects."

More laboratory work is needed to prove a causal relationship, not a mere correlation, between telomere length and aging or cancer, the researchers say. Only then will they know whether human telomeres respond to the same signals as yeast, potentially leading to medical treatments and dietary guidelines. For now, Prof. Kupiec suggests, "Try to relax and drink a little coffee and a little beer."

***http://www.eurekalert.org/pub_releases/2013-12/ncsu-dtt120513.php***

## Database tracks toxic side effects of pharmaceuticals

***Sometimes the cure can be worse than the disease.***

Pharmaceutical drugs are known for their potential side effects, and an important aspect of personalized medicine is to tailor therapies to individuals to reduce the chances of adverse events. Now researchers from North Carolina State University have updated an extensive toxicology database so that it can be used to track information about therapeutic drugs and their unintentional toxic effects.

"Environmental science actually shares a common goal with drug makers: to improve the prediction of chemical toxicity," says Dr. Allan Peter Davis, lead author of a paper on the work and the biocuration project manager of the Comparative Toxicogenomics Database (CTD) in NC State's Department of Biological Sciences.

The scientific literature contains vast information about the adverse effects of therapeutic drugs. But collecting, organizing and making sense of that published information is a daunting task. NC State's CTD team, which historically focused on environmental chemicals, read and coded more than 88,000 scientific papers for this effort.

It took the CTD team one year to efficiently extract information from those 88,000 papers about therapeutic drugs and their involvement in toxic endpoints, such as hypertension, seizures, kidney failure and liver disease.

"The project quickly added lots of new data that complements environmental toxicity," says Davis.

The results include more than 250,000 statements collected from seven decades' worth of scientific articles. Putting the data into the CTD framework helps investigators develop and test hypotheses about how drugs might cause adverse events.

"Coding the information in a structured format was key," insists Davis. "This allowed it to be combined with other data to make novel predictions." For example, the drug bortezomib is used to treat certain types of cancer, but it also causes unintended nerve damage in some patients. By linking the data, CTD was able to connect the dots and find genes that that may be key to connecting the drug and the possibility of nerve damage.

"Investigators can now test and validate which genes might be critical to the drug-induced event," explains Davis. "This could be useful in gene-testing patients to tailor the correct medicine or it could help design future therapeutics by alerting safety researchers to avoid those pathways and potential toxic outcomes."

The CTD group also designed a new phenotype module. In this context, phenotypes are events that happen in a cell or system before the toxicity or full-blown disease is recognized at the clinical level. Drugs can affect phenotypes as well as diseases. Independently coding drug-disease and drug-phenotype interactions from the literature and then storing them in the same database allows the system to connect certain phenotypes to diseases, based upon their shared drugs. These connections may allow scientists to resolve, and ultimately *prevent, how chemicals – from the environment or from the medicine cabinet – cause toxicity.*

*The paper, "A CTD-Pfizer collaboration: manual curation of 88,000 scientific articles text mined for drug-disease and drug-phenotype interactions," is published online in the journal Database. Co-authors include NC State software engineer Thomas Wiegers; NC State biocurators Drs. Jean Lay, Kelley Lennon-Hopkins and Daniela Sciaky; Dr. Carolyn Mattingly, an*

*associate professor of biological sciences at NC State; Drs. Phoebe Roberts, Nigel Greene, Robert Hernandez, Kevin McConnell, and Ahmed Enayetallah of Pfizer; and Drs. Robin Johnson and Heather Keating, and Benjamin King from The Mount Desert Island Biological Laboratory. The work was supported by Pfizer, Inc. and the National Institute of Environmental Health Sciences.*

***http://www.sciencedaily.com/releases/2013/12/131205141309.htm***

# Emerging Bird Flu Strain Poorly Adapted for Infecting Humans

***H7N9 virus has not yet acquired the changes needed to infect humans easily,***

Avian influenza virus H7N9, which killed several dozen people in China earlier this year, has not yet acquired the changes needed to infect humans easily, according to a new study by scientists at The Scripps Research Institute (TSRI). In contrast to some initial studies that had suggested that H7N9 poses an imminent risk of a global pandemic, the new research found, based on analyses of virus samples from the Chinese outbreak, that H7N9 is still mainly adapted for infecting birds, not humans.

"Luckily, H7N9 viruses just don't yet seem well adapted for binding to human receptors," said Ian A. Wilson, the Hansen Professor of Structural Biology and chair of the Department of Integrative Structural and Computational Biology at TSRI.

"Because publications to date have implied that H7N9 has adapted to human receptors, we felt we should make a clear statement about this," said James C. Paulson, chair of TSRI's Department of Cell and Molecular Biology.

The Wilson and Paulson laboratories collaborated on the study, which is reported in the December 6, 2013 issue of the journal Science.

**A Worrisome Outbreak**

H7N9 flu viruses infect birds, apparently causing them few or no symptoms. Until this year these strains had never been reported in humans. However, starting in February in two urban areas of eastern China, dozens of people began to come down with H7N9 flu. Most became severely ill. By the end of May, when the outbreak had mostly subsided, there were 132 laboratory-confirmed human cases and 37 deaths -- a nearly 30% case-fatality rate.

The outbreak understandably alarmed public health officials, and across the globe dozens of laboratories began studying H7N9 isolates from infected patients. The big question was whether these strains were capable of spreading only in a limited, sporadic way from birds to humans -- many of the cases were linked to poultry exposure -- or if they had truly "jumped the species barrier." If the latter were true, and H7N9 could now spread from human to human, the Chinese outbreak might be the start of a global pandemic.

Some prominent early studies came to worrisome conclusions. For example, most of the H7N9 isolates from the outbreak turned out to have acquired a notorious flu-virus mutation that substitutes the amino acid leucine for glutamine in the part of the virus that grabs receptors on host cells. The same mutation, in other influenza virus subtypes, was apparently a key enabler of pandemics that killed an estimated one million people worldwide in 1968-69 (the "Hong Kong flu") and two million during 1957-58 (the "Asian flu"). Initial studies of the new H7N9 isolates in mice, ferrets and monkeys also suggested that they had at least a limited ability to spread among mammals.

**Answering Critical Questions**

Paulson's and Wilson's laboratories, long experienced in flu virus and immunity research, were among the many that mobilized to try to answer the crucial question of H7N9's transmissibility among humans. They quickly decided to collaborate. Paulson's laboratory evaluated H7N9's ability to bind the sialylated sugar receptors to which flu viruses normally attach on host cells. Wilson's laboratory used X-ray crystallography to determine the atomic structures of the H7N9 hemagglutinin protein bound to these sialic acid receptor molecules.

Paulson's team -- including postdoctoral fellows Robert P. de Vries and Corwin M. Nycholat and Research Assistant Ryan McBride -- tested the ability of the virus's hemagglutinin (HA) protein, to bind to different human and avian receptor variants. These tests showed clearly that the isolate tested (A/Shanghai/2/2013 or "Sh2") still has a strong preference for avian-type receptors and binds human-type receptor variants only weakly.

In Wilson's laboratory, postdoctoral fellow Rui Xu, the study's first author, along with Staff Scientist Xueyong Zhu and Research Assistant Wenli Yu, performed X-ray crystallography studies of the Sh2 HA protein bound to several avian- and human-type receptors. The latter, provided by Paulson's laboratory, were more accurate versions of these receptors than any that had been used in previous H7N9 structural analyses.

The new data highlighted the looseness of the contacts that Sh2 HA makes with human-type receptors, in contrast to the snug couplings it makes with certain avian-type receptors.

Thus, despite hints that it had begun to adapt to human hosts rather than its natural bird hosts, H7N9 does not appear to pose an imminent threat of a human pandemic. "These results suggest that we should continue to

observe H7N9 and see if it undergoes any changes that make it more likely to spread in the human population," said Wilson. Paulson added, "If it does evolve a true human-type receptor specificity, it could potentially spread among humans much better than it does now."

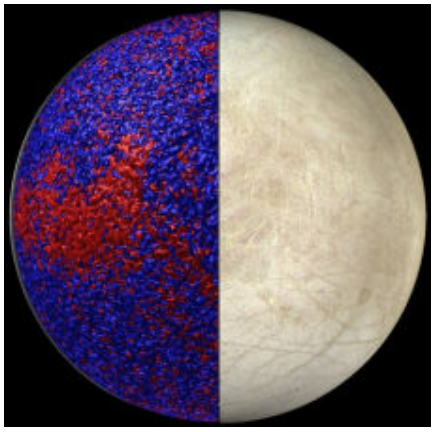
*James C. Paulson, Ian A. Wilson et al. Preferential Recognition of Avian-Like Receptors in Human Influenza A H7N9 Viruses. Science, December 2013 DOI: 10.1016/science.1243761*

***http://arstechnica.com/science/2013/12/europas-ocean-could-help-explain-its-jigsaw-surface/***

## Europa's ocean could help explain its jigsaw surface

***Models try to puzzle through the moon's icy shell to the ocean beneath it.***

**by Scott K. Johnson - Dec 6 2013, 9:00pm TST**



Part of the beauty of Jupiter's icy moon Europa is its incredible smoothness. But like most things, if you look closely, cracks appear in this facade. In Europa's case, the cracks come in the form of jumbled pieces of ice that make up what are called the moon's "chaos terrains." Just what caused the chaos is an open question.

There is, however, an obvious candidate. Europa's most exciting characteristic is probably the ocean of liquid water that is thought to exist beneath that icy crust. It seems likely that the ocean has something to do with the chaos terrain, especially given the presence of salt there. To figure that out, however, we'd have to know something about how water circulates in that ocean. And, unlike our own oceans, you can't just chuck a buoy in and see where it goes.

***A snapshot from the model on the left, showing warmer and cooler water. Image of Europa's surface on the right.*** **J. Wicht and NASA/JPL/University of Arizona**

Circulation in the ocean would be driven by the heat from Europa's interior. It's been thought that the big-picture pattern might look something like the atmosphere of Jupiter, with alternating bands of eastward or westward flow. Ultimately, this pattern carries the greatest amount of internal heat to Europa's polar regions. A new study, led by University of Texas at Austin researcher Krista Soderlund, suggests the circulation pattern could actually look quite different.

The researchers created a mathematical model of Europa's ocean that could simulate the Jupiter-like circulation pattern. Then, they played with a key parameter in the equations—a term known as the Rossby number. It has to do with how strongly the Coriolis effect—the force that causes air to spiral in toward the low pressure at the center of a hurricane—influences the flow of the ocean water.

Estimates for what value of the Rossby number best represents the conditions on Europa have varied, but only the smaller values produce a Jupiter-like circulation pattern. By using a larger value in their model, the researchers push the circulation pattern into a very different configuration.

The flow is a little more complex, and the neatly separated bands of eastward and westward flow break down. It's a little less Jupiter-like and a little more like Earth's atmosphere.

On Earth, a convection cell in the tropics carries air upwards at the equator and back down around 30 degrees north and south latitude. That same kind of behavior shows up in the ocean in this model, with a Coriolis-induced westward component to the flow, just like the trade winds on Earth. At high latitudes, the simulated water flows in the opposite direction.

Most importantly, heat is distributed much differently. Rather than warming the poles most, warm water generally rises at the equator, with cool water sinking at the poles.

That's intriguing, because the chaos terrains mostly exist between 40 degrees south and north of Europa's equator. If this picture of Europa's circulation is accurate, it would seemingly link the delivery of heat to the underside of Europa's icy shell near the equator, which could then lead to the unknown process that forms the chaos terrain.

In an accompanying article, Wheaton College astronomer Jason Goodman laments the difficulty of studying Europa's intriguing subsurface. "If we hope to directly sample Europa's ocean, traversing the last few kilometers of ice may prove a greater challenge than crossing a billion kilometers of interplanetary space. In the meantime, indirect observations and computer simulations continue to provide new insights into this mysterious alien ocean."

*Nature Geoscience, 2013. DOI: 10.1038/NGEO2021, 10.1038/NGEO2034 (About DOIs).*

http://www.eurekalert.org/pub_releases/2013-12/uocd-crm120613.php

## CU researchers may have discovered a plan to disable Meniere's disease

***Researchers at University of Colorado School of Medicine may have figured out what causes Meniere's disease and how to attack it.***

AURORA, Colo - According to Carol Foster, MD, from the department of otolaryngology and Robert Breeze, MD, a neurosurgeon, there is a strong association between Meniere's disease and conditions involving temporary low blood flow in the brain such as migraine headaches.

Meniere's affects approximately 3 to 5 million people in the United States. It is a disabling disorder resulting in repeated violent attacks of dizziness, ringing in the ear and hearing loss that can last for hours and can ultimately cause permanent deafness in the affected ear. Up until now, the cause of the attacks has been unknown, with no theory fully explaining the many symptoms and signs of the disorder.

"If our hypothesis is confirmed, treatment of vascular risk factors may allow control of symptoms and result in a decreased need for surgeries that destroy the balance function in order to control the spell" said Foster. "If attacks are controlled, the previously inevitable progression to severe hearing loss may be preventable in some cases." Foster explains that these attacks can be caused by a combination of two factors: 1) a malformation of the inner ear, endolymphatic hydrops (the inner ear dilated with fluid) and 2) risk factors for vascular disease in the brain, such as migraine, sleep apnea, smoking and atherosclerosis.

The researchers propose that a fluid buildup in part of the inner ear, which is strongly associated with Meniere attacks, indicates the presence of a pressure-regulation problem that acts to cause mild, intermittent decreases of blood flow within the ear. When this is combined with vascular diseases that also lower blood flow to the brain and ear, sudden loss of blood flow similar to transient ischemic attacks (or mini strokes) in the brain can be generated in the inner ear sensory tissues. In young people who have hydrops without vascular disorders, no attacks occur because blood flow continues in spite of these fluctuations. However, in people with vascular diseases, these fluctuations are sufficient to rob the ear of blood flow and the nutrients the blood provides. When the tissues that sense hearing and motion are starved of blood, they stop sending signals to the brain, which sets off the vertigo, tinnitus and hearing loss in the disorder.

Restoration of blood flow does not resolve the problem. Scientists believe it triggers a damaging after-effect called the ischemia-reperfusion pathway in the excitable tissues of the ear that silences the ear for several hours, resulting in the prolonged severe vertigo and hearing loss that is characteristic of the disorder. Although most of the tissues recover, each spell results in small areas of damage that over time results in permanent loss of both hearing and balance function in the ear.

Since the first linkage of endolymphatic hydrops and Meniere's disease in 1938, a variety of mechanisms have been proposed to explain the attacks and the progressive deafness, but no answer has explained all aspects of the disorder, and no treatment based on these theories has proven capable of controlling the progression of the disease. This new theory, if proven, would provide many new avenues of treatment for this previously poorly-controlled disorder.

*The article is available online at: The Meniere attack: An ischemia/reperfusion disorder of inner ear sensory tissues, Medical Hypotheses, December 2013.*

http://www.eurekalert.org/pub_releases/2013-12/uob-hsc120613.php

## Human stem cells predict efficacy of Alzheimer drugs

***Researchers from the University of Bonn use reprogrammed patient neurons for drug testing***

Why do certain Alzheimer medications work in animal models but not in clinical trials in humans? A research team from the University of Bonn and the biomedical enterprise LIFE & BRAIN GmbH has been able to show that results of established test methods with animal models and cell lines used up until now can hardly be translated to the processes in the human brain. Drug testing should therefore be conducted with human nerve cells, conclude the scientists. The results are published by Cell Press in the journal "Stem Cell Reports".

In the brains of Alzheimer patients, deposits form that consist essentially of beta-amyloid and are harmful to nerve cells. Scientists are therefore searching for pharmaceutical compounds that prevent the formation of these dangerous aggregates. In animal models, certain non-steroidal anti-inflammatory drugs (NSAIDs) were found to a reduced formation of harmful beta-amyloid variants. Yet, in subsequent clinical studies, these NSAIDs failed to elicit any beneficial effects.

"The reasons for these negative results have remained unclear for a long time", says Prof. Dr. Oliver Brüstle, Director of the Institute for Reconstructive Neurobiology of the University of Bonn and CEO of LIFE & BRAIN GmbH. "Remarkably, these compounds were never tested directly on the actual target cells – the human neuron", adds lead author Dr. Jerome Mertens of Prof. Brüstle's team, who now works at the Laboratory of Genetics in La Jolla (USA). This is because, so far, living human neurons have been extremely difficult to

obtain. However, with the recent advances in stem cell research it has become possible to derive limitless numbers of brain cells from a small skin biopsy or other adult cell types.

**Scientists transform skin cells into nerve cells**

Now a research team from the Institute for Reconstructive Neurobiology and the Department of Neurology of the Bonn University Medical Center together with colleagues from the LIFE & BRAIN GmbH and the University of Leuven (Belgium) has obtained such nerve cells from humans. The researchers used skin cells from two patients with a familial form of Alzheimer's Disease to produce so-called induced pluripotent stem cells (iPS cells), by reprogramming the body's cells into a quasi-embryonic stage. They then transformed the resulting so-called "jack-of-all-trades cells" into nerve cells.

Using these human neurons, the scientists tested several compounds in the group of non-steroidal anti-inflammatory drugs. As control, the researchers used nerve cells they had obtained from iPS cells of donors who did not have the disease. Both in the nerve cells obtained from the Alzheimer patients and in the control cells, the NSAIDs that had previously tested positive in the animal models and cell lines typically used for drug screening had practically no effect: The values for the harmful beta-amyloid variants that form the feared aggregates in the brain remained unaffected when the cells were treated with clinically relevant dosages of these compounds.

**Metabolic processes in animal models differ from humans**

"In order to predict the efficacy of Alzheimer drugs, such tests have to be performed directly on the affected human nerve cells", concludes Prof. Brüstle's colleague Dr. Philipp Koch, who led the study. Why do NSAIDs decrease the risk of aggregate formation in animal experiments and cell lines but not in human neurons? The scientists explain this with differences in metabolic processes between these different cell types. "The results are simply not transferable", says Dr. Koch.

The scientists now hope that in the future, testing of potential drugs for the treatment of Alzheimer's disease will be increasingly conducted using neurons obtained from iPS cells of patients. "The development of a single drug takes an average of ten years", says Prof. Brüstle. "By using patient-specific nerve cells as a test system, investments by pharmaceutical companies and the tedious search for urgently needed Alzheimer medications could be greatly streamlined".

*Publication: APP Processing in Human Pluripotent Stem Cell-Derived Neurons is Resistant to NSAID-Based Gamma-Secretase Modulation, Stem Cell Reports, DOI: 10.1016/j.stemcr.2013.10.011*

***http://www.eurekalert.org/pub_releases/2013-12/uosd-sdt120613.php***

## Surprising discovery: The skin communicates with the liver

***Researchers from the University of Southern Denmark have discovered that the skin is capable of communicating with the liver.***

The discovery has surprised the scientists, and they say that it may help our understanding of how skin diseases can affect the rest of the body. Professor Susanne Mandrup and her research group in collaboration with Nils Færgeman's research group at the Department of Biochemistry and Molecular Biology at the University of Southern Denmark was actually studying something completely different when they made the groundbreaking discovery: That the skin, which is the body's largest organ, can "talk" to the liver.

"We have showed that the skin affects the metabolism in the liver, and that is quite a surprise", say Susanne Mandrup and Ditte Neess, a former student in the Mandrup research group and now laboratory manager in Professor Nils Færgeman's group.

The phenomenon was observed in the researcher's laboratory mice. The Mandrup and Færgeman groups work with so-called knock-out mice, in which a specific fat binding protein called acyl CoA binding protein has been removed (knocked out). Some knock-out mice produced by the researchers had a strange greasy fur, and they had difficulties being weaned from their mother. In the weaning period they gained less weight and showed a failure to thrive. Analyses also showed that the mice accumulated fat in the liver at weaning.

"At first we thought that the fat accumulation in the liver was linked with the fact that the gene was missing in the liver of the knock-out mice. But this was ruled out by a series of studies, and we had to find another explanation", says Ditte Neess.

She and her colleagues took another look at the rumpled and weak knock-out mice. Their fur was greasy, and they had a leaky skin from which they lost more water than normal mice. "When they lose water, they also lose heat. We therefore asked ourselves whether this water and heat loss could be the reason why the mice accumulated fat in the liver and became weak when weaned from their mother", says Ditte Neess.

To clarify this, the researchers made some mice that lacked the fat binding protein only in the skin. Similar to the full knockouts these mice had difficulties after weaning and accumulated fat in the liver. So this showed that the lack of the fat-binding protein in the skin was sufficient to induce accumulation of fat in the liver.

To get to the bottom of how a defect in the skin "talks" to the liver, the researchers decided to cover the mice with vaseline. This would prevent water evaporating from the skin and thus stopping the heat loss. As a result the fat accumulation in the liver disappeared. But as vaseline contains fat, that could theoretically be absorbed by the skin or ingested by the mice, the researchers were a little unsure if there were side effects from the vaseline. A student proposed to cover the mice with liquid latex, which she found in a local sex shop.
Having covered the mice in blue latex the researchers saw that fat accumulation in the liver again disappeared. "We believe that the leaking of water from the skin makes the mice feel cold, and that this leads to breaking down of fat in their adipose (fat) tissue. The broken down fat is then moved to the liver. The mice move energy from the tissues to the liver", Susanne Mandrup and Ditte Neess explain.

*Ref: Ditte Neess, Signe Bek, Maria Bloksgaard, Ann-Britt Marcher, Nils J. Færgeman, Susanne Mandrup: Delayed Hepatic Adaptation to Weaning in ACBP/Mice Is Caused by Disruption of the Epidermal Barrier. Cell Report. Dec 5 2013.*

***http://www.eurekalert.org/pub_releases/2013-12/mg-nsf120513.php***

## New study finds corn oil superior to extra virgin olive oil in lowering cholesterol

***Plant sterols naturally found in corn oil linked to heart health benefits***

Washington - Corn oil significantly reduces cholesterol with more favorable changes in total cholesterol (TC) and LDL-C than extra virgin olive oil, new research shows. The findings were presented today at the American Society for Nutrition's Advances & Controversies in Clinical Nutrition Conference by lead researcher, Dr. Kevin C Maki, PhD, of Biofortis, the clinical research arm of Mérieux NutriSciences.

Among the 54 healthy men and women in the feeding study, consumption of foods made with corn oil resulted in significantly lower levels of LDL (bad) cholesterol and total cholesterol than the same foods made with extra virgin olive oil. Corn oil lowered LDL cholesterol by 10.9 percent compared to extra virgin olive oil's 3.5 percent reduction1,2, and total cholesterol decreased by 8.2 percent with corn oil compared to 1.8 percent for extra virgin olive oil.2 Study participants received four tablespoons of corn oil or extra virgin olive oil in the foods provided every day, consistent with the Dietary Guidelines for Americans recommendations. All foods were provided to the study participants as part of a weight maintenance diet.

The randomized, double-blind, controlled crossover clinical trial assessed the effects of dietary oils on fasting lipoprotein lipids. The study compared the effects of corn and extra virgin olive oil on LDL cholesterol (primary outcome variable), total cholesterol, HDL cholesterol (good cholesterol), Non-HDL cholesterol, Triglycerides and the total to HDL cholesterol ratio. Study participants had fasting LDL cholesterol ≥130 mg/dL and <200 mg/dL. Fasting blood samples, along with other clinical measurements, were taken from all participants during visits to the clinical study center before and after each treatment phase of the study. "The study results suggest corn oil has significantly greater effects on blood cholesterol levels than extra virgin olive oil, due, in part, to the natural cholesterol-blocking ability of plant sterols," said Dr. Maki. "These findings add to those from prior research supporting corn oil's positive heart health benefits."

Cardiovascular disease remains the number one cause of death in the United States. Existing research supports the notion diets containing at least 5-10 percent of calories from polyunsaturated fatty acids (PUFAs) from vegetable oils, are associated with lower risk for heart disease.4

Corn oil has a unique combination of healthy fatty acids and plant sterols, which research suggests help lower cholesterol.4,5 Corn oil has four times more plant sterols than olive oil and 40 percent more than canola oil.6 Based on analysis of corn oil and 2013 USDA comparison of other cooking oils, corn oil has a plant sterols content of 135.6 mg/serving vs. 30.0 mg/serving for olive oil.7 Plant sterols are plant-based substances naturally present in fruits, vegetables, nuts, seeds, cereals, legumes and vegetable oils, such as corn oil. To the extent that plant sterols play a part in reducing blood cholesterol levels, they could have an important role in a heart healthy diet.

***http://www.medscape.com/viewarticle/817372?src=rss***

## Response to a Single Question May Flag Suicide Risk

***A specific response to a single question from a commonly used depression scale may help clinicians flag patients at increased risk for suicide, new research suggests.***

**Deborah Brauser**

A study of more than 84,000 patients with depressive symptoms who completed the Patient Health Questionnaire (PHQ-9) at every outpatient visit for depression care during a 4-year period showed that respondents who reported that they thought about death or self-harm "nearly every day" had more than a 6-fold increased risk for suicide attempt compared with respondents who did not consider these options.

According to investigators, led by Gregory E. Simon, MD, MPH, from the Group Health Research Institute in Seattle, Washington, patients who reported thoughts of death or self-harm "more than half the days" or "nearly every day" accounted for 53% of suicide attempts and 54% of suicide deaths.

Interestingly, the immediate risk for suicidal behavior after completing the PHQ-9 was low, but the risk increased during several days and continued to grow for several months after.
"Suicidal ideation should be viewed as an enduring vulnerability rather than simply a short-term crisis," write the investigators. "These findings emphasize the need for sustained and organized follow-up care to address ongoing risk."
The study was published in the December issue of Psychiatric Services.

**A Leading Cause of Death**

According to the investigators, in 2010 there were 38,000 suicide deaths in the United States, making suicide the 10th leading cause of death. In addition, suicide attempts have led to approximately 200,000 annual hospitalizations and 600,000 visits to emergency departments (EDs).
"Early intervention to reduce this morbidity and mortality would require both accurate screening tests and effective interventions for persons found to be at risk," write the researchers.
They add that, before their study, no evidence had shown that a screening could accurately identify this at-risk population. "Consequently, the US Preventive Services Task Force and others do not recommend screening for risk of suicidal behavior," the investigators report.
"Nevertheless, increasing use of standard depression outcome questionnaires means that clinicians treating depression will frequently encounter patients who report thoughts of death or self- harm."
For the study, investigators evaluated electronic health record data from 84,418 individuals who were part of the Group Health Cooperative, a large, integrated healthcare system serving the states of Washington and Idaho. All participants were older than 12 years; they completed 207,265 PHQ-9s from January 2007 to January 2011 as part of outpatient treatment for depression during visits to primary care or mental health speciality providers. Patient data were then linked to insurance claims and death certificates reporting suicide attempts or suicide deaths.

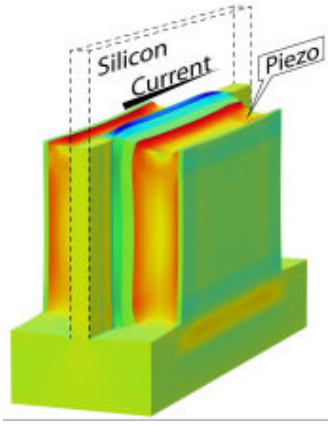
**Suicide Deaths, Attempts**

Item 9 on the PHQ-9 specifically asks, "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?" Answer options were "not at all," "several days," "more than half the days," or "nearly every day."
Results showed that there were 46 suicide deaths and 709 nonfatal suicide attempts among all of the participants. Of the suicide attempts, 371 led to hospitalization and 338 led to ED or outpatient treatment.
Of the total group assessed, 77% answered "not at all" to item 9 on the PHQ-9, 14% answered "several days," 5% answered "more than half the days," and 4% answered "nearly every day."
Those responding "nearly every day" had a relative hazard ratio (HR) of 6.37 for suicide attempt (95% confidence interval [CI], 5.07 - 8.01) compared with those who responded "not at all." Those who responded with "more than half the days" had a relative HR of 4.12 (95% CI, 3.34 - 5.08).
Further analysis showed a significant "linear relationship between item 9 score and risk of subsequent suicide attempt, with a 91% increase in risk…for each one-step increase in reported frequency of thoughts of death or self-harm" (HR, 1.91; 95% CI, 1.79 - 2.04; $P < .001$), report the investigators.
The relative HR for suicide death in participants who responded with "nearly every day" to item 9 was 5.28 (95% CI, 2.14 - 13.03) compared with those who responded "not at all"; it was 5.89 (95% CI, 3.14 - 11.08) for those who responded with "more than half the days."
"Wide confidence limits for HRs reflect the small numbers of suicide deaths," explain the researchers.
There was also a significant ($P < .001$) linear relationship between subsequent suicide death and item 9 score, with an HR of 1.92 (95% CI, 1.53 - 2.41) for each increased step in suicidal thought frequency.
Practical Guidance for Everyday Practice
The investigators note that because the PHQ-9 was designed to measure depression severity and not suicidal behavior specifically, the wording of item 9 could lead to the false inclusion or exclusion of certain patients. Instead, using a measurement that was specifically created for suicidal ideation could be potentially more accurate in predicting these risks. "This report, however, intends to provide practical guidance regarding a measure that is widely and increasingly used in everyday practice."
They add that although the results do not justify population-based screening, it is important to note that in a measurement that is already commonly used, 1 in 10 of the participants reported thoughts of death or self-harm at least half of their days.
"And those patients experienced a markedly increased risk of subsequent suicide attempt and suicide death. For this high-risk group, additional assessment is clearly indicated," write the researchers.
The study was funded by the National Institute of Mental Health. The study authors have disclosed no relevant financial relationships. *Psychiatr Serv. 2013;64:1195-1202.* *Abstract*

http://www.sciencedaily.com/releases/2013/12/131206091423.htm

## Squeezing Transistors Really Hard Generates Energy Savings

***If silicon is squeezed, this affects the freedom of movement of the electrons in this material.***




This can promote or restrict the flow of electrical current. Compare it to a garden hose. When you stand on it, less water comes out. But strangely enough, the flow of electrons in silicon actually increases when the material is compressed.

**Only pinch when necessary**

In modern microchips, every single transistor is continuously exposed to enormous pressures of up to 10,000 atmospheres. This pressure is sealed in during the manufacturing process, by surrounding the transistors with compressive materials. While this boosts the chip's processing speed, the leakage current also increases. The use of piezoelectric material means that the transistors are only put under pressure when this is necessary. This can generate considerable savings in terms of energy consumption.

***The electrical current passing through a transistor is conducted by a slice of silicon. In the new transistor, this is sandwiched between layers of piezoelectric material. As this material (shown in red) expands, the silicon (shown in blue) is compressed.*** **(Credit: Image courtesy of University of Twente)**

**Limit smashed**

The underlying concept was originally developed by Ray Hueting. In order to turn this into reality, Tom van Hemert had to find a way of linking theories of mechanical deformation with quantum-mechanical formulas describing the electrical behaviour of transistors. The calculations indicate that "garden hose transistors" are much better than conventional transistors at switching from off to on. According to the classical theoretical limit, a charge of at least 60 millivolts is needed to make a transistor conduct ten times more electricity. The piezoelectric transistor uses just 50 millivolts. As a result, either the leakage current can be reduced, or more current can be carried in the on-state. Either way, this will boost the performance of modern microchips, while -- importantly -- cutting their energy consumption.

The results of this research were recently published in the journal, Transactions on Electron Devices.

http://www.livescience.com/41758-earth-magnetic-field-magma-ocean.htm

## Magma Ocean Could Have Given Early Earth Magnetic Field

***Earth may have possessed a magnetic field shortly after its birth, suggesting that magnetic shielding could have played a larger role in the development of life on Earth than currently thought, researchers say in a new study.***

**By Charles Q. Choi, LiveScience Contributor | December 06, 2013 11:26am ET**

Nowadays, churning that occurs in Earth's liquid outer core creates the dynamo that generates Earth's magnetic field. This churning, known as convection, happens because of heat flow — electrically conductive molten iron alloy in the core's outer layer gets hot and rises, then dissipates this heat and sinks.

Investigations of ancient rocks suggest Earth has possessed a magnetic field for at least the past 3.5 billion years of its 4.6-billion-year history. Earth's magnetic field leaves an imprint on magnetically sensitive minerals in cooling lava, literally setting in stone the direction the planet's magnetic poles were aimed when the rocks formed.

However, recent experiments hint Earth's core might not have been able to generate a magnetic field until about 2.1 billion years ago. These studies suggested the amount of heat flowing out of the core needs to be nearly three times greater than once thought to create enough convection to generate a dynamo. The core could not sustain this huge amount of heat flow for the entire 3.5-billion-year history of Earth's magnetic field.

In the new study, researchers suggest Earth's first magnetic field may not have originated from the planet's core as it does today, but from a giant ocean of magma sitting on top of the core.

Moreover, this magma ocean may have given Earth a magnetic field beginning 4.5 billion years ago, some 1 billion years earlier than Earth is currently suspected to have possessed a magnetic field.

"If the model is correct, it shatters nearly every assumption about the early Earth," study author Dave Stegman, a geophysicist at the University of California, San Diego, told LiveScience's OurAmazingPlanet.

'Far-reaching consequences'

Past research suggested a magma ocean might have existed in the lowermost part of Earth's mantle layer between the core and crust from very early in Earth's history. This ocean would have existed from about 4.5 billion years ago to at least about 2.5 billion years ago. Oregon State University geophysicist and study co-

author Leah Ziegler read about how a magma ocean within Jupiter's moon Io might influence Jupiter's magnetic field and wondered if Earth's ancient magma ocean could have generated a magnetic field.
Ziegler and Stegman modeled a range of electrical and magnetic properties that molten silicate rock in this magma ocean might have possessed. The researchers found that the molten rock's electrical conductivity might have been high enough to drive a dynamo early in Earth's history.
"The most important implication is that the Earth's early magnetic field was not generated in the core as has always been previously thought, but rather from inside the mantle," Stegman said.
If Earth had a magnetic field shortly after its birth, "this could have far-reaching implications," Stegman added. For example, if Earth had magnetic shielding from the sun that early on, this may have had consequences for the development of life on Earth.
"The first living cells on Earth may have first appeared 3.5 billion years ago, so perhaps the origin of life was related to the stable surface environment allowed by [the] protection of a magnetic field around Earth," Stegman said. "Magnetic shielding would also protect the atmosphere from being eroded away by the solar wind."
It remains uncertain if silicate liquids at the extreme pressures and temperatures found in this magma ocean would have been electrically conductive enough to drive a dynamo. The researchers plan to test their idea with a more sophisticated model of magnetic field generation.
"If our next results are also favorable, that should provide enough impetus for other disciplines to more seriously consider investigating this model," Stegman said.
*Ziegler and Stegman detailed their findings online Nov. 26 in the journal Geochemistry, Geophysics, Geosystems.*

***http://www.medscape.com/viewarticle/817371?src=rss***

## FDA Approves 'Game Changer' Hepatitis C Drug Sofosbuvir

***Food and Drug Administration has approved the first-in-kind nuceotide analog inhibitor sofosbuvir for the treatment of adults with chronic HCV***

**Miriam E. Tucker**

The US Food and Drug Administration (FDA) has approved the first-in-kind nuceotide analog inhibitor sofosbuvir (Sovaldi, Gilead Sciences, Inc) for the treatment of adults with chronic hepatitis C virus (HCV) infection, a widely anticipated move that is expected to dramatically improve outcomes for many patients.
Data presented earlier this year at an FDA advisory committee meeting support the use of sofosbuvir in combination with ribavirin (RBV) for all-oral dual therapy of infections with HCV genotypes 2 and 3, as well as in triple therapy along with injected pegylated interferon (pegIFN) and RBV for treatment-naive patients with HCV genotypes 1 and 4.
The availability of the first all-oral, interferon-free regimen is a first and a major advance, experts say.
"This is a very exciting time in liver diseases," Greg Fitz, MD, president of the American Association for the Study of Liver Diseases, said at a news conference held last month during The Liver Meeting 2013, at which sofosbuvir was discussed extensively and new data were presented.
"I think the move away from interferon and toward a high probability of success is remarkably encouraging for all of us.... Suddenly, it's realistic to think we can cure most patients with hepatitis C," Dr. Fitz told reporters.
"Sofosbuvir is a game-changer and will allow high cure rates with just 12-week regimens," David R. Nelson, MD, assistant vice president for research, professor of medicine, and associate dean of clinical research at the College of Medicine, University of Florida, Gainesville, told Medscape Medical News.
Indeed, liver expert Norah A. Terrault, MD, told Medscape Medical News that sofosbuvir holds numerous advantages over current therapy because of its efficacy profile, safety, and tolerability across many different patient populations and HCV genotypes, as well as its dosing simplicity.
"And of course, the first all-oral option for patients with HCV is also a large step forward in terms of principal, to show that you can eradicate HCV without interferon being part of the treatment cocktail.... It's a huge and major advance," said Dr. Terrault, professor of medicine and surgery and director of the Viral Hepatitis Center at the University of California, San Francisco.
Data supporting licensure for sofosbuvir came from 6 clinical trials consisting of 1947 participants, some in trials of sofosbuvir plus RBV with HCV genotype 2 or 3 (including both treatment-naive patients and those who had failed or could not tolerate previous therapy) and others taking the triple combination of sofosbuvir, RBV, and pegIFN in 3 treatment-naive patients infected with HCV genotypes 1, 4, 5, or 6.
At the advisory committee hearing, Gilead scientists reported sustained viral clearance at 12 weeks (SVR12) ranging from 89% to 95% for genotype 2 and 61% to 63% for genotype 3. For HCV genotype 1, which accounts for about 70% of all HCV in the United States, sofosbuvir-based triple therapy including pegIFN produced an SVR12 of 89%.

Dr. Terrault noted that although there has been a published trial showing efficacy of sofosbuvir and RBV without IFN for HCV genotype 1, the SVR12 was inferior to the triple therapy regimen.

**New Treatment Options**

Dr. Terrault suggested that patients with HCV genotypes 2 and 3 who have been "warehoused" waiting for the new sofosbuvir-based regimens can begin treatment immediately.

For HCV genotypes 1, 4, and 6, whether or not to begin using sofosbuvir-based therapy depends on the situation. For patients who do not have severe liver disease, waiting is still an option.

At least 4 companies are working on interferon-free regimens that are expected to be available for genotype 1. "We're not talking 10 years away, we're talking about 18 months," she told Medscape Medical News.

"Unless a patient has advanced liver disease, one has the luxury of time to wait for good therapies to come forward, to find the right one for the patient…. With this very rapidly evolving field of therapeutics, we should be thoughtful about when we intervene. We should be doing it with the goal of treating them once and with the highest likelihood of success. And we know that over the next couple of years, the proportion that's going to be successful will go up and the ease of treatment will be increased," Dr. Terrault predicted.

However, for patients with genotype 1 who have advanced liver disease (stage 3 or 4), the triple combination of sofosbuvir/IFN/RBV is now an option, as is the off-label combination of sofosbuvir plus the newly licensed simeprevir.

Dr. Terrault noted that although the ultimate goal is to move toward IFN-free regimens, IFN does have the advantage of shortening the treatment time to just 12 weeks. "There's a lot of enthusiasm for IFN-free, and for sure it's the way the field is going...but in the interim we have sofosbuvir for genotype 1 approved with pegIFN and RBV, so it's reasonable to discuss that option."

Dr. Nelson pointed out that although the combination of sofosbuvir with simeprevir (with or without ribavirin) is not yet FDA-approved, phase 2 data presented at The Liver Meeting showed SVR12 rates greater than 90% in genotype 1 patients.

"Given the recent...phase 2 data, there will be great interest to combine sofosbuvir and simeprevir in all-oral regimens for genotype 1 patients. This may also be the preferred regimen for post-liver transplant," he told Medscape Medical News.

**Cost Considerations**

Addressing the issue of cost, announced to be about $80,000 per treatment course, Dr. Terrault said it is important to factor in other contributors such as additional monitoring and treatment of adverse effects that are expected to be lower with sofosbuvir. "It's not just a matter of cost per pill.... The cost per cure is what you want to see."

In a study presented at The Liver Meeting, the cost per SVR of current telaprevir-based triple therapy at 1 institution was calculated to be $189,000.

Dr. Terrault told Medscape Medical News, "There will be a competitive market of all-oral drugs in the future. I would predict that as the years go by and we have more all-oral combinations coming to market, it will ultimately result in less expensive options for patients. It may not be in the next year, but over time it will help to have therapy become less costly and maybe then more broadly applicable, not just in the US but in terms of the world market."

Dr. Fitz has disclosed no relevant financial relationships. Dr. Nelson has research relationships with both Gilead and Janssen. Dr. Terrault has received grant support from Gilead, Novartis, and Abbvie and has consulted for BMS and Janssen.

***http://www.eurekalert.org/pub_releases/2013-12/nion-csu120613.php***

## Concussion secrets unveiled in mice and people

***NIH scientists film early concussion damage and describe brain's response to injury***

There is more than meets the eye following even a mild traumatic brain injury. While the brain may appear to be intact, new findings reported in Nature suggest that the brain's protective coverings may feel the brunt of the impact.

Using a newly developed mouse trauma model, senior author Dorian McGavern, Ph.D., scientist at the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health, watched specific cells mount an immune response to the injury and try to prevent more widespread damage. Notably, additional findings suggest a similar immune response may occur in patients with mild head injury.

In this study, researchers also discovered that certain molecules, when applied directly to the mouse skull, can bypass the brain's protective barriers and enter the brain. The findings suggested that, in the mouse trauma model, one of those molecules may reduce effects of brain injury.

Although concussions are common, not much is known about the effects of this type of damage. As part of this study, Lawrence Latour, Ph.D., a scientist from NINDS and the Center for Neuroscience and Regenerative Medicine, examined individuals who had recently suffered a concussion but whose initial scans did not reveal any physical damage to brain tissue. After administering a commonly used dye during MRI scans, Latour and his colleagues saw it leaking into the meninges, the outer covers of the brain, in 49 percent of 142 patients with concussion.

To determine what happens following this mild type of injury, researchers in Dr. McGavern's lab developed a new model of brain trauma in mice.

"In our mice, there was leakage from blood vessels right underneath the skull bone at the site of injury, similar to the type of effect we saw in almost half of our patients who had mild traumatic brain injury. We are using this mouse model to look at meningeal trauma and how that spreads more deeply into the brain over time," said Dr. McGavern.

Dr. McGavern and his colleagues also discovered that the intact skull bone was porous enough to allow small molecules to get through to the brain. They showed that smaller molecules reached the brain faster and to a greater extent than larger ones. "It was surprising to discover that all these protective barriers the brain has may not be concrete. You can get something to pass through them," said Dr. McGavern.

The researchers found that applying glutathione (an antioxidant that is normally found in our cells) directly on the skull surface after brain injury reduced the amount of cell death by 67 percent. When the researchers applied glutathione three hours after injury, cell death was reduced by 51 percent. "This idea that we have a time window within which to work, potentially up to three hours, is exciting and may be clinically important," said Dr. McGavern.

Glutathione works by decreasing levels of reactive oxygen species (ROS) molecules that damage cells. In this study, high levels of ROS were observed at the trauma site right after the physical brain injury occurred. The massive flood of ROS set up a sequence of events that led to cell death in the brain, but glutathione was able to prevent many of those effects.

In addition, using a powerful microscopic technique, the researchers filmed what was happening just beneath the skull surface within five minutes of injury. They captured never-before-seen details of how the brain responds to traumatic injury and how it mobilizes to defend itself.

Initially, they saw cell death in the meninges and at the glial limitans (a very thin barrier at the surface of the brain that is the last line of defense against dangerous molecules). Cell death in the underlying brain tissue did not occur until 9-12 hours after injury. "You have death in the lining first and then this penetrates into the brain tissue later. The goal of therapies for brain injury is to protect the brain tissue," said Dr. McGavern.

Almost immediately after head injury, the glial limitans can break down and develop holes, providing a way for potentially harmful molecules to get into the brain. The researchers observed microglia (immune cells that act as first responders in the brain against dangerous substances) quickly moving up to the brain surface, plugging up the holes.

Findings from Dr. McGavern's lab indicate that microglia do this in two ways. According to Dr. McGavern, "If the astrocytes, the cells that make up the glial limitans, are still there, microglia will come up to 'caulk' the barrier and plug up gaps between individual astrocytes. If an astrocyte dies, that results in a larger space in the glial limitans, so the microglia will change shape, expand into a fat jellyfish-like structure and try to plug up that hole. These reactions, which have never been seen before in living brains, help secure the barrier and prevent toxic substances from getting into the brain."

Studies have suggested that immune responses in the brain can often lead to severe damage. Remarkably, the findings in this study show that the inflammatory response in a mild traumatic brain injury model is actually beneficial during the first 9-12 hours after injury.

Mild traumatic brain injuries are a growing public health concern. According to a report from the Centers of Disease Control and Prevention, in 2009 at least 2.4 million people suffered a traumatic brain injury and 75 percent of those injuries were mild. This study provides insight into the damage that occurs following head trauma and identifies potential therapeutic targets, such as antioxidants, for reducing the damaging effects.

*Theodore L. Roth et al. "Transcranial amelioration of inflammation and cell death following brain injury," Nature, December 8, 2013.*