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Master switch found to stop tumor cell growth by inducing dormancy

Two existing cancer drugs turn on a gene that tells tumor cells to remain inactive

Two existing cancer drugs turn on a gene that tells tumor cells to remain inactive, according to a study led by researchers at the Icahn School of Medicine at Mount Sinai and published today in Nature Communications.

Researchers discovered that the gene NR2F1, when switched on, programs tumor cells to stay dormant. When the gene is switched off, tumor cells divide and multiply as part of abnormal growth, potentially allowing dormant cells to grow into tumors throughout the body (metastasis). Combining the anticancer drugs azacytidine and retinoic acid significantly increased the amount of active NR2F1 in tumor cells. These patterns were found in mouse models of several cancers, and confirmed in prostate cancer cells from human patients.

Results suggest that NR2F1 is a "master regulator" of tumor cell growth, influencing several genes that determine whether cells remain inactive, or quiescent in medical terms. According to the study, NR2F1 exerts control over long lasting programs in stem cells in the human embryo, where it directs cells to stop growing and become specialized cells (neurons) for life. This function suggests that NR2F1 may exert a long-lasting effect on tumor cells, keeping them dormant after they have broken off from an original tumor.

"Our results explain why some tumor cells scattered through the body are committed to remaining harmless for years, while others cause active disease," said Julio A. Aguirre-Ghiso, PhD, Professor of Medicine, Hematology and Medical Oncology, and Otolaryngology at the Icahn School of Medicine. "In finding this master switch we found a way to analyze tumor cells before treatment to determine the risk of a cancer recurrence or metastasis."

"Azacytidine and retinoic acid, the latter a form of vitamin A, prevented tumor cells from rapidly multiplying, restored normal cell function, and activated several tumor suppressor genes that are often turned off in tumors," said study co-leader Maria Soledad Sosa, PhD, a postdoctoral fellow in Hematology at the Icahn School of Medicine. "We now have strong evidence that combining these well-known drugs may have a profound, long-lasting therapeutic effect."

The current study builds on the research team's earlier finding that lowering amounts of tumor suppressor genes TGFβ2 and p38 awakened dormant tumor cells, fueling metastatic tumor growth. Azacytidine and retinoic acid restored TGFβ2 expression and p38 activation to drive tumor cell dormancy.

This study was supported by grants from the Samuel Waxman Cancer Research Foundation, National Cancer Institute, National Institute of Environmental Health Sciences, New York State Stem Cell Science program, JJR Foundation and Hirschl/Weill-Caulier Trust, Department of Defense and Janssen Research and Development LLC.

http://bit.ly/1F9lgGP

Why We Can Thank Bats for Bedbugs

Scientists have proven through genetics that bats were the first hosts to the pesky parasite before passing them on to ancient humans

By Laura Clark

Though they're the cause of many recent nightmares, bedbugs have been keeping people awake at night for thousands of years. Archeologists in Egypt once found a 3,500-year-old fossilized specimen of the skin-crawling parasite. There are also writings from ancient Greece and Rome that mention the bloodsuckers.

Now, a paper recently published in the journal *Molecular Ecology* has zeroed in on just where bedbugs first came from. The research "provides the first genetic evidence that bats were the ancestral host of the bed bugs that plague human residences today," reports Melissa Hogenboom over at BBC Earth.

Scientists have previously suspected that bats were responsible for introducing bedbugs to the human population, back when the two species both made caves their home: bats are known to be plagued by their own member of the bedbug family. The new research, co-authored by Dr. Warren Booth of the University of Tulsa, appears to confirm this theory. It also determines that the two parasites feeding on bats and humans respectively have evolved into two separate lineages without much interchange.

Writes Hogenboom:

Booth's team sampled hundreds of bed bugs from human and bat dwellings from 13 countries around Europe.

An analysis of their DNA showed that there was no gene flow occurring between the human and bat bed bugs, even though some bats lived in churches or attics and could therefore have come into human contact.

Bat bugs, as they are colloquially referred to, are fairly common to North America but typically only bother humans when their animal hosts have fled. Booth told BBC Earth that bat bugs are more genetically diverse and are so different from the human-feeding kind that, when interbred, "the offspring were less fertile."

Bedbug populations are resurging in many parts of the world after decades of near-eradication. That's in part because the parasites have developed a resistance to the pesticides used to rid them from our homes and hotel rooms beginning in the 1950s. According to data collected by Orkin and cited by *Time*, the business

around getting rid of bedbugs increased 18 percent last year, and in 2013, Americans spent $446 million on the effort.

There's some good news, though: despite being gross and ruining property, bedbugs have not been shown to transmit diseases. But perhaps that knowledge won't keep you from checking your mattress before getting into bed tonight.

http://www.eurekalert.org/pub_releases/2015-02/nsf-epr020215.php

Expert panel recommends new sleep durations

National Sleep Foundation completes rigorous study and updates recommended sleep times at each life stage

WASHINGTON, DC - The National Sleep Foundation (NSF), along with a multi-disciplinary expert panel, issued its new recommendations for appropriate sleep durations. The report recommends wider appropriate sleep ranges for most age groups. The results are published in *Sleep Health: The Official Journal of the National Sleep Foundation*.

The National Sleep Foundation convened experts from sleep, anatomy and physiology, as well as pediatrics, neurology, gerontology and gynecology to reach a consensus from the broadest range of scientific disciplines. The panel revised the recommended sleep ranges for all six children and teen age groups. A summary of the new recommendations includes:

- ***Newborns (0-3 months): Sleep range narrowed to 14-17 hours each day (previously it was 12-18)***
- ***Infants (4-11 months): Sleep range widened two hours to 12-15 hours (previously it was 14-15)***
- ***Toddlers (1-2 years): Sleep range widened by one hour to 11-14 hours (previously it was 12-14)***
- ***Preschoolers (3-5): Sleep range widened by one hour to 10-13 hours (previously it was 11-13)***
- ***School age children (6-13): Sleep range widened by one hour to 9-11 hours (previously it was 10-11)***
- ***Teenagers (14-17): Sleep range widened by one hour to 8-10 hours (previously it was 8.5-9.5)***
- ***Younger adults (18-25): Sleep range is 7-9 hours (new age category)***
- ***Adults (26-64): Sleep range did not change and remains 7-9 hours***
- ***Older adults (65+): Sleep range is 7-8 hours (new age category)***

"This is the first time that any professional organization has developed age-specific recommended sleep durations based on a rigorous, systematic review of the world scientific literature relating sleep duration to health, performance and safety," said Charles A. Czeisler, PhD, MD, chairman of the board of the National Sleep Foundation, chief of sleep and circadian disorders at Brigham and Women's Hospital, and Baldino Professor of Sleep Medicine at the Harvard Medical School.

"The National Sleep Foundation is providing these scientifically grounded guidelines on the amount of sleep we need each night to improve the sleep health of the millions of individuals and parents who rely on us for this information."

A new range, "may be appropriate," has been added to acknowledge the individual variability in appropriate sleep durations. The recommendations now define times as either (a) recommended; (b) may be appropriate for some individuals; or (c) not recommended.

"The National Sleep Foundation Sleep Duration Recommendations will help individuals make sleep schedules that are within a healthy range. They also serve as a useful starting point for individuals to discuss their sleep with their health care providers," said David Cloud, CEO of the National Sleep Foundation.

National Sleep Foundation's Sleep Duration Recommendations:

Age	Recommended	May be appropriate	Not recommended
Newborns	14 to 17 hours	11 to 13 hours	Less than 11 hours
0-3 months		18 to 19 hours	More than 19 hours
Infants	12 to 15 hours	10 to 11 hours	Less than 10 hours
4-11 months		16 to 18 hours	More than 18 hours
Toddlers	11 to 14 hours	9 to 10 hours	Less than 9 hours
1-2 years		15 to 16 hours	More than 16 hours
Preschoolers	10 to 13 hours	8 to 9 hours	Less than 8 hours
3-5 years		14 hours	More than 14 hours
School-aged Children	9 to 11 hours	7 to 8 hours	Less than 7 hours
6-13 years		12 hours	More than 12 hours
Teenagers	8 to 10 hours	7 hours	Less than 7 hours
14-17 years		11 hours	More than 11 hours
Young Adults	7 to 9 hours	6 hours	Less than 6 hours
18-25 years		10 to 11 hours	More than 11 hours
Adults	7 to 9 hours	6 hours	Less than 6 hours
26-64 years		10 hours	More than 10 hours
Older Adults	7 to 8 hours	5 to 6 hours	Less than 5 hours
≥ 65 years		9 hours	More than 9 hours

The recommendations are the result of multiple rounds of consensus voting after a comprehensive review of published scientific studies on sleep and health. The expert panel included six sleep experts and experts from the following stakeholder organizations:

- American Association of Anatomists - American Academy of Pediatrics
- American College of Chest Physicians - American Geriatrics Society
- American Neurological Association - American Physiological Society
- American Psychiatric Association - American Thoracic Society
- Gerontological Society of America - Human Anatomy and Physiology Society

- Society for Research in Human Development - American Congress of Obstetricians and Gynecologists

"The NSF has committed to regularly reviewing and providing scientifically rigorous recommendations," says Max Hirshkowitz, PhD, Chair of the National Sleep Foundation Scientific Advisory Council. "The public can be confident that these recommendations represent the best guidance for sleep duration and health."

To view the full results and methodology of the report, please visit sleephealthjournal.org.

http://www.eurekalert.org/pub_releases/2015-02/bcfg-met020215.php

More evidence that musical training protects the brain

Scientists have found some of the strongest evidence yet that musical training in younger years can prevent the decay in speech listening skills in later life.

Toronto, CANADA - According to a new Canadian study led by the Rotman Research Institute (RRI) at Baycrest Health Sciences, older adults who had musical training in their youth were 20% faster in identifying speech sounds than their non-musician peers on speech identification tests, a benefit that has already been observed in young people with musical training.

The findings are published in The Journal of Neuroscience (Jan. 21).

Among the different cognitive functions that can diminish with age is the ability to comprehend speech. Interestingly, this difficulty can persist in the absence of any measurable hearing loss. Previous research has confirmed that the brain's central auditory system which supports the ability to parse, sequence and identify acoustic features of speech - weakens in later years.

Starting formal lessons on a musical instrument prior to age 14 and continuing intense training for up to a decade appears to enhance key areas in the brain that support speech recognition. The Rotman study found "robust" evidence that this brain benefit is maintained even in the older population.

"Musical activities are an engaging form of cognitive brain training and we are now seeing robust evidence of brain plasticity from musical training not just in younger brains, but in older brains too," said Gavin Bidelman, who led the study as a post-doctoral fellow at the RRI and is now an assistant professor at the University of Memphis.

"In our study we were able to predict how well older people classify or identify speech using EEG imaging. We saw a brain-behaviour response that was two to three times better in the older musicians compared to non-musicians peers. In other words, old musicians' brains provide a much more detailed, clean and accurate depiction of the speech signal, which is likely why they are much more sensitive and better at understanding speech."

Bidelman received a GRAMMY Foundation research grant to conduct the study and partnered with senior scientist Claude Alain, assistant director of Baycrest's RRI and a leading authority in the study of age-related differences in auditory cortical activity.

The latest findings add to mounting evidence that musical training not only gives young developing brains a cognitive boost, but those neural enhancements extend across the lifespan into old age when the brain needs it most to counteract cognitive decline. The findings also underscore the importance of music instruction in schools and in rehabilitative programs for older adults.

In this study, 20 healthy older adults (aged 55-75) - 10 musicians and 10 non-musicians - put on headphones in a controlled lab setting and were asked to identify random speech sounds. Some of the sounds were single vowel sounds such as an "ooo" or an "ahhh", others more ambiguous as a mix of two sounds that posed a greater challenge to their auditory processing abilities for categorizing the speech sound correctly.

During the testing cycles, researchers recorded the neural activity of each participant using electroencephalography (EEG). This brain imaging technique measures to a very precise degree the exact timing of the electrical activity which occurs in the brain in response to external stimuli. This is displayed as waveforms on a computer screen. Researchers use this technology to study how the brain makes sense of our complex acoustical environment and how aging impacts cognitive functions.

According to Bidelman and Alain's published paper, the older musicians' brain responses showed "more efficient and robust neurophysiological processing of speech at multiple tiers of auditory processing, paralleling enhancements reported in younger musicians."

Bidelman is currently collaborating with Alain and the RRI on a randomized training study in older adults to assess if these benefits emerge with short-term music intervention.

http://www.eurekalert.org/pub_releases/2015-02/uouh-iom013015.php

Identification of much-needed drug target against MRSA, gram-positive infections

The increasing prevalence of antibiotic resistance, when infectious bacteria evolve to evade drugs designed to control them, is a pressing public health concern.

Each year two million Americans acquire antibiotic-resistant infections, leading to 23,000 deaths. In light of these unsettling statistics, there has been a call to develop new weapons to combat bacterial threats to human health.

Scientists at the University of Utah and the University of Georgia have uncovered a pharmacological target that could enable development of novel drugs against antibiotic-resistant pathogens, including Methicillin-resistant Staphylococcus aureus (MRSA) and other infectious Gram-positive organisms such as Listeria

and Mycobacterium tuberculosis. The target was revealed upon discovery of a Gram-positive bacteria-specific pathway for making heme, an essential iron-carrying molecule. The findings were reported in the journal, Proceedings of the National Academy of Sciences (PNAS).

"The therapeutic target could be used to create a completely new class of drugs for fighting Gram-positive bacteria including those that cause antibiotic-resistant infections," says John Phillips, Ph.D., senior author of the paper and research professor in hematology at the University of Utah School of Medicine.

The fortuitous discovery was an outcome of a quest to solve a case of mistaken identity. For the past 100 years, the prevailing notion was that every organism - from bacteria to man - used the same eight-step recipe to make the essential, snowflake-shaped iron transporter, heme. That's why Harry Dailey, Ph.D., first author and biochemistry professor at the University of Georgia, was puzzled when he noticed that proteins that were given the name HemN, a key component of the historically-defined heme pathway, looked very different in Gram-positive bacteria than in other classes of bacteria. The code of amino acids - building blocks of proteins - that were recorded as Gram-positive "HemN" didn't match up with the rest.

"It made me wonder, 'What do we know, as opposed to what do we think we know?'" recalled Harry Dailey, Ph.D., first author and professor of biochemistry at the University of Georgia.

In the lab, he found that the so-called Gram-positive bacteria "Heme N" was, in fact, incapable of making heme. Determined to figure out what substitutes for HemN, Dailey collaborated with Phillips to purify components of the heme pathway in Gram-positive bacteria. Like figuring out how to make a cake by seeing how it looks after each step of the recipe is completed, they collected the intermediates of the heme pathway, and determined that the last three were completely different than expected. Biochemical experiments further showed that a Gram-positive specific enzyme called HemQ is required for the final step. A survey of heme pathway components in over 350 other organisms support the idea that only Gram-positive bacteria use the alternate, HemQ-dependent recipe for making heme.

The implications were immediately obvious to Dailey and Phillips. "A drug that disables HemQ, will knock out heme biosynthesis only in Gram-positive bacteria, sparing this important pathway in our own cells," explains Dailey. He has already demonstrated that genetically eliminating HemQ severely disables the troublesome germs, suggesting a drug that targets the protein will do the same. If screens against existing compounds identify one that is capable of blocking HemQ, a drug could be available in as quickly as two years; development of a new antibiotic could take ten years.

"The original goal of this work was to sort out the naming of different bacterial genes, but the result was identifying a completely new metabolic pathway that can be exploited to improve healthcare," says Phillips. "It's a reminder that, to paraphrase Louis Pasteur, chance favors the prepared mind."

The study was supported by the National Institutes of Health.

Co-authors include Tamara Dailey and Joseph Burch of the University of Georgia, and Svetlana Gerdes of the Argonne National Laboratory.

***Noncanonical coproporphyrin-dependent bacterial heme biosynthesis pathway that does not use protoporphyrin**. PNAS Early Edition, Feb. 2, 2015*

http://www.eurekalert.org/pub_releases/2015-02/nu-lso013015.php

Language study offers new twist on mind-body connection

Research from Northeastern professor of psychology Iris Berent and her colleagues finds that spoken language and motor systems are intricately linked - though not in the way that has been widely believed

New research from Northeastern professor of psychology Iris Berent and her colleagues indicates that language and motor systems are intricately linked - though not in the way that has been widely believed.

Spoken languages express words by sound patterns, some of which are preferred to others. For instance, the sound pattern "blog" is preferred to "lbog" in English as well as many other languages. The researchers wanted to know what accounts for such preferences - specifically, whether they reflect abstract rules of language in the brain, or if upon hearing speech people attempt to simulate how those sounds are produced by the speech motor system.

Their findings support previous research indicating the connection between people's knowledge of language and the motor system; however, that connection is different than what has been previously assumed. The motor system doesn't drive linguistic preference directly, they found. Rather, abstract rules of language guide linguistic preference, and these abstract rules can trigger motor action. In other words, motor action is a consequence of - not the cause of - linguistic preference.

Sound patterns like "blog" are preferred over those like "lbog" not because they are easy to produce; rather, these syllables are preferred because they conform to linguistic rules, and consequently they tend to activate the motor system, she said.

What's more, Berent said these findings could have implications in studying language-related disorders that are linked to the motor system. One of those areas is dyslexia, which Berent has been studying for years.

"This has huge theoretical implications," said Berent, a cognitive scientist whose research examines the nature of linguistic competence. "The idea that linguistic knowledge is fully embodied in motor action is a hot topic in neuroscience right now. Our study shows that motor action is still very important in language processing, but we show a new twist on the mind-body connection."

The research was published Monday afternoon in the journal Proceedings of the National Academy of Sciences. Among Berent's collaborators was Alvaro Pascual-Leone, an internationally renowned neurologist at Beth Israel Deaconess Medical Center in Boston and Harvard Medical School and whose expertise in transcranial magnetic stimulation, or TMS, played a key role in the research. Xu Zhao, PhD'15, a doctoral student in Northeastern's Department of Psychology, and other researchers affiliated with the Beth-Israel Deaconess Medical Center, Harvard Medical School, Brigham and Women's Hospital, and University of Oxford co-authored the paper.

Albert Galaburda, a co-author on the paper and a preeminent neurologist at BIDMC, said, "This study helps to solve a longstanding debate in the literature: What part of speech depends on experience and what part depends on relatively experience-independent grammatical rules, or some kind of logic system? Since my primary interest is in language-based learning disorders, particularly dyslexia, this question can be transformed to ask whether dyslexics have a primary disorder of grammar, or a primary disorder of experience with language, as in poor perception of speech reaching their ears when babies."

The researchers' findings are based on a study in which they sought to gauge the sensitivity of English-speaking adults to syllable structure. Across languages, syllables like "blif" are more common than "lbif," and past research from Berent's lab found that syllables like "blif" are easier to process, suggesting that these syllables are preferred. The researchers sought to discover the reason for this preference: do ill-formed syllables like "lbif" violate abstract rules, or do people have difficulty in their processing because these syllables are hard to produce?

To examine this question, the researchers used TMS, a noninvasive technique that induces focal cortical current via electro-magnetic induction to temporarily inhibit specific brain regions. The goal was to find out if disrupting participants' lip motor regions using TMS would eliminate the preference for "blif."

In the experiment, participants were presented with an auditory stimulus - either a monosyllable or disyllable, for example "blif" or "belif" - and asked to indicate if that stimulus included one or two syllables. Two hundred milliseconds before hearing that sound, TMS pulses were administered to temporarily disrupt the lip motor region. The critical comparison concerned well-formed syllables (e.g., "blif") vs. ill-formed ones (e.g., "lbif"). The researchers asked whether the disruption of the motor system would disrupt the disadvantage of "lbif." If people dislike "lbif" because this pattern is difficult to articulate, then syllables like "lbif" should be more susceptible to TMS, and therefore once people receive the TMS, their dislike for "lbif" should be lessened.

They found that TMS pulses did impair participants' ability to accurately determine the number of syllables. However, the results flew in the face of the embodiment motor hypothesis. The researchers found that ill-formed syllables like "lbif" were least likely to be impaired by TMS, and a subsequent functional MRI experiment found that these syllables were also least likely to engage the lip motor area in the brain.

The results show that speech perception automatically engages the articulatory motor system, but linguistic preferences persist even when the language motor system is disrupted. These findings suggest that, despite their intimate links, the language and motor systems are distinct.

"Language is designed to optimize motor action, but its knowledge consists of principles that are disembodied and potentially abstract," the researchers concluded.

http://www.eurekalert.org/pub_releases/2015-02/uopa-asi012815.php

A simple intervention can make your brain more receptive to health advice

New research into the effects of self-affirmation

A new discovery shows how a simple intervention - self-affirmation - can open our brains to accept advice that is hard to hear.

"Self-affirmation involves reflecting on core values," explained Emily Falk, the study's lead author and director of the Communication Neuroscience Laboratory at University of Pennsylvania's Annenberg School for Communication. Has your doctor ever told you to get more exercise? Has your spouse ever suggested you eat healthier? Even though the advice comes from good intentions, most people feel defensive when confronted with suggestions that point out their weaknesses. Reflecting on values that bring us meaning can help people see otherwise threatening messages as valuable and self-relevant. "Our work shows that when people are affirmed, their brains process subsequent messages differently."

Along with colleagues at Annenberg, The University of Michigan and The University of California Los Angeles, Falk and her team used functional magnetic resonance imaging (fMRI) to examine a part of the brain involved in processing self-relevance called ventromedial prefrontal cortex (VMPFC). The team examined activity in this region as sedentary adults were given the type of advice they might get from a doctor (e.g. - "People who sit less are at lower risk for

certain diseases."). Participants who were guided through a self-affirmation exercise before getting the health advice showed higher levels of activity in this key brain region during the health advice, and then went on to show a steeper decline in couch-potato-type sedentary behaviors in the month following the intervention. Those who were instructed to think about values that weren't as important to them showed lower levels of activity in the key brain region during exposure to the health advice and maintained their original levels of sedentary behavior. The results are reported in the February of the Proceedings of the National Academy of Science.

Past studies have shown that brain activity in VMPFC during health messages can predict behavior change better than individuals' own intentions, and this study sheds new light on why. VMPFC is the brain region most commonly activated when participants think about themselves and when they ascribe value to ideas. The new results show that opening the brain in this way is a key pathway to behavior change. "Understanding the brain opens the door to new health interventions that target this same pathway," Falk noted.

"We were particularly interested in using self-affirmation to help people become more active because sedentary behavior is one of the biggest health threats faced by both Americans and people around the world," said Falk. Overly sedentary lifestyles are becoming a big problem; in some regions nearly 85 percent of an adult population leads an inactive lifestyle. This can cause multiple health problems, including poor heart health, diabetes, and cancer, just to name three. Increasing activity even small amount can have an important impact on both mental and physical health.

The team studied 67 sedentary adults from a range of backgrounds. Participants wore devices on their wrists to objectively measure their activity levels for a week before and a month after the intervention. Participants were also sent text messages reinforcing the main messages delivered in the fMRI scanner. Volunteers were shown health messages like "According to the American Heart Association, people at your level of physical inactivity are at much higher risk for developing heart disease," or "After an hour of sitting, try standing for five minutes. Stand up while you read, watch TV, talk on the phone, fold laundry, or write an email." For some participants, these health messages were packaged with a self-affirmation message like "think of a time when you will help a friend or family member reach an accomplishment." When health messages were paired with self-affirmation, volunteers demonstrated more activity in VMPFC activity during the health message and also went on to follow the advice more.

Psychologists have used self-affirmation as a technique to improve outcomes ranging from health behaviors in high risk patients to increasing academic performance in at risk youth, suggesting that the findings may be applicable across a wide range of interventions. "Our findings highlight that something as simple as reflecting on core values can fundamentally change the way our brains respond to the kinds of messages we encounter every day," Falk noted. "Over time, that makes the potential impact huge."

The research team included Professor Falk, Matthew Brook O'Donnell (Annenberg), Christopher N. Cascio (Annenberg), Francis Tinney (University of Michigan), Yoona Kang (Annenberg), Matthew D. Lieberman (UCLA), Shelley Taylor (UCLA), Lawrence An (University of Michigan), Kenneth Resnicow (University of Michigan), and Victor Strecher (University of Michigan).

http://www.eurekalert.org/pub_releases/2015-02/cmaj-cua012815.php

Commonly used antibiotics with diuretic can double risk of sudden death in older patients

Combination of a commonly prescribed antibiotic with a diuretic widely used for heart failure more than doubles the risk of death for older patients

The combination of the commonly prescribed antibiotic trimethoprim-sulfamethoxazole with the diuretic spironolactone, widely used for heart failure, more than doubles the risk of death for older patients, reports a study published in CMAJ (Canadian Medical Association Journal).

Trimethoprim-sulfamethoxazole is frequently prescribed for urinary tract infections, with more than 20 million prescriptions written every year in the United States for a variety of infections. Spironolactone is effective for heart failure, but it can raise blood potassium to potentially life-threatening levels in some patients.

The large study, conducted over a 17-year period, involved 206 319 patients aged 66 years or older who were treated with spironolactone. Of these, 11 968 people died suddenly and 328 of these died within 14 days after taking either trimethoprim-sulfamethoxazole, amoxicillin, ciprofloxacin, norfloxacin or nitrofurantoin. Most of the patients who died were over age 85 and those who received trimethoprim-sulfamethoxazole were more likely to die than those who took amoxicillin.

"Sudden death during spironolactone treatment was more than twice as likely following a prescription for trimethoprim-sulfamethoxazole than for amoxicillin," writes lead author Dr. Tony Antoniou of the Li Ka Shing Knowledge Institute, St. Michael's Hospital and the Institute for Clinical Evaluative Sciences (ICES), Toronto, Ontario, with coauthors.

"More attention needs to be given to the real risk that trimethoprim-sulfamethoxazole can incite life-threatening hyperkalemia in susceptible individuals," said Dr. Antoniou. "And the risks increase when these antibiotics are

prescribed with other medications that raise blood potassium, such as spironolactone," he added.

The authors suggest that, when appropriate, physicians should consider prescribing different antibiotics for patients on spironolactone, limiting the duration of antibiotic treatment and carefully monitoring to reduce the risk of death.

http://www.eurekalert.org/pub_releases/2015-02/uosc-rmc020215.php

Rivers might constitute just 20 percent of continental water flowing into oceans

Subterranean estuary could outpace rivers in both volume and nutrient content

If you think rivers are what send terrestrial rainfall back into the oceans, you don't know the half of it. And that fraction keeps shrinking. According to new research, it might be that only one-fifth of the water flowing from the continents into the Atlantic and Indo-Pacific Oceans runs through overland channels of water. And just as surprising, a vast amount flows into the land from the ocean.

University of South Carolina professor Willard Moore is part of an international team that recently estimated how much of the water flowing into the oceans comes not from surface rivers, creeks and streams, but instead from what he has termed the "subterranean estuary."

For two decades, Moore has drawn attention to the oft-overlooked flow and exchange of ocean and groundwater in the permeable layers of rock and sediment, a process that occurs both near the coastline and extending out on the continental shelf. But the roots of his work in the field go back even further in his 50-year scientific career.

Developing the tools of the trade

Soon after earning a doctorate at the State University of New York at Stony Brook, Moore began working in the early 1970s as a civilian in the Naval Oceanographic Office, then located in Maryland. The task at hand was to study deep ocean processes, and one of the best tools for doing that was to measure the amounts of certain naturally occurring radioactive elements dissolved in the seawater at different locations and depths.

"There's a little bit of uranium and thorium in all rocks, and as those elements decay, they produce a whole string of different elements, which themselves are radioactive," Moore says. "So say a rock is in seawater and the uranium decays to thorium and then it decays to radium. Well, the radium is much more soluble than the other components, so it can go into solution in the seawater. There are very few ways to remove it naturally, except by radioactive decay."

Moore likens the radium that dissolves from a rock to a dye that slowly loses its intensity over time. The half-life of radium establishes how fast the "dye" loses intensity, and by measuring how radium concentrations diminish with increasing distance from the seafloor - the rock source - a scientist can come up with a model for how the water there is flowing and mixing.

A major shortcoming at the time, though, was how laborious it was to collect data. Radioactive elements are present in very small concentrations in seawater.

"It used to be that you needed about 600 to 800 liters of water," amounting to more than 200 gallons for a single data point, Moore says. "It was a very time-consuming series of chemical processes, and I decided early on that if we were really going to use radium to understand the ocean, we had to have a better way to extract it."

From Lake Oneida to the sea

Moore put together a new method after mulling over a few disparate observations. Some colleagues had come up with a much more efficient means for extracting a different radioactive isotope, silicon-32, by coating an acrylic fiber with an iron compound and then exposing it to flowing seawater. Silica (which contains silicon-32) in the water is adsorbed onto the fiber, effectively concentrating the radionuclide into a much smaller area (namely, on the surface of the fiber rather than dispersed in many gallons of water).

The iron coating on the fiber didn't pick up radium, but Moore found something that did while working on a small side project. He was trying to understand the growth of a characteristic kind of rock formation found in certain places on the bottom of Lake Oneida, a freshwater lake of glacial origin in central New York. The formation is called a manganese nodule, which has alternating layers rich in manganese and iron oxides.

In the course of that research, he found that the nodules were rich in radium as well, which put him on the idea that perhaps manganese dioxide could be used to extract radium from seawater.

"I remember very clearly when I saw the first counts on the radium in the nodule. I walked into the lab, mixed up a manganese solution, and put it on the fiber," Moore says. "I was living on Chesapeake Bay and had a sailboat, so I went out, towed it through the bay, came back and it was loaded with radium. It's just an illustration of how if you have several irons in the fire, they all don't get hot at the same time, but sometimes one will ignite another one."

Putting the tools to work

Moore joined the Carolina faculty in 1976 with a ready means of determining radium concentration in seawater, and he expanded his repertoire from the deep-sea research that characterized his work with the Navy to closer-to-shore studies.

A primary goal in South Carolina was to understand the exchange processes between water and surface sediments in estuaries near the coastline.

Much of the early work with radium, though, raised all sorts of questions, Moore says. The gradients they were seeing simply didn't make sense, but in retrospect it was because one basic assumption was way off.

At the time, it was generally thought that groundwater flow into the ocean was insignificant, maybe 3 percent to 5 percent of river flow, Moore says. The breakthrough came when one of his colleagues suggested that a sizable salty groundwater flow must be responsible for their observations.

They measured radium in inland wells, finding that fresh groundwater had almost none, but that saltier groundwater was loaded with it. The inescapable conclusion: water from the ocean was being exchanged with groundwater in prodigious quantities, and it was happening underground.

"The action was in the permeable sediments below. It started this whole idea that the continents were connected to the ocean not only by riverine processes, but by submarine processes." Moore says. "I came up with the term subterranean estuary. So just like the surface estuary, it's the region between the coast and the ocean where freshwater is coming in on one side and seawater is coming in on the other side, they're mixing, and after chemical reactions, some of that water is expelled back into the ocean."

Moore was part of an international team that developed a quantitative model for submarine groundwater discharge across most of the globe, and they just published a paper in Geophysical Research Letters showing that the amount of subterranean water flow into the Atlantic and Indo-Pacific Oceans is some three to four times that of all rivers combined.

Perhaps even more important is the conclusion that most of the flow of terrestrial nutrients is subterranean.

"If you put a lot of nutrients into the ocean, you increase primary productivity. You make lots of algae, which may be good, but excessive algae settles out and as it decays it uses up oxygen from the bottom water," Moore says. "We call it hypoxia, where the oxygen is so low fish can't breathe. So, productivity is a delicate balance.

"Currently, in most of the estimates of how nutrients come into the water, it's thought to be coming from rivers, springs, streams - things you can see - or from point source pollution, sewage, drainage pipes off of golf courses. But people have not considered how much is coming from the subterranean estuary. It's a whole biogeochemical process that's going on that people haven't really thought about very much."

http://www.eurekalert.org/pub_releases/2015-02/mc-wbc012915.php

Which breast cancer patients need lymph nodes removed?

Ultrasound narrows it down, study finds

Rochester, Minn. - Which breast cancer patients need to have underarm lymph nodes removed? Mayo Clinic-led research is narrowing it down. A new study finds that not all women with lymph node-positive breast cancer treated with chemotherapy before surgery need to have all of their underarm nodes taken out. Ultrasound is a useful tool for judging before breast cancer surgery whether chemotherapy eliminated cancer from the underarm lymph nodes, the researchers found. The findings are published in the Journal of Clinical Oncology.

In the past, when breast cancer was discovered to have spread to the lymph nodes under the arm, surgeons routinely removed all of them. Taking out all of those lymph nodes may cause arm swelling called lymphedema and limit the arm's range of motion.

Now, many breast cancer patients receive chemotherapy before surgery. Thanks to improvements in chemotherapy drugs and use of targeted therapy, surgeons are seeing more women whose cancer is eradicated from the lymph nodes by the time they reach the operating room, says lead author Judy C. Boughey, M.D. a breast surgeon at Mayo Clinic in Rochester.

The current study finds that repeating ultrasound after chemotherapy is a sound way to help determine whether surgeons should remove only a few lymph nodes and test them for cancer, sparing patients whose sentinel nodes are cancer-free the removal of all nodes in the armpit, or take out all of the nodes, Dr. Boughey says.

"Our goal here is really to try to get away from, 'Every patient with breast cancer needs these drugs, and this amount of chemotherapy and this surgery,' and instead to personalize surgical treatment based on how the patient responds to chemotherapy," Dr. Boughey says.

Avoiding complete underarm lymph node removal when possible means fewer women will experience the complications that can accompany that surgery, and avoiding those side effects should also save health care costs, she says.

"That's one of the really nice things about giving chemotherapy up front: It allows us to be less invasive with surgery, both in terms of breast surgery and lymph node surgery, and to tailor treatment based on response to chemotherapy," Dr. Boughey says.

Most patients with lymph node-positive breast cancer receive radiation treatment after surgery. A new study is under way for men and women with breast cancer whose underarm lymph nodes are still positive for cancer after chemotherapy. It will evaluate which is more effective: removing all of those nodes, or leaving the nodes and treating them with radiation, Dr. Boughey says.

The current research was supported by National Cancer Institute grants U10 CA76001 to the American College of Surgeons Oncology Group, CA31946 to the Alliance for Clinical Trials in Oncology and CA33601 to the Alliance Statistics and Data Center.

The study's senior author is Huong T. Le-Petross, M.D., of MD Anderson Cancer Center in Houston. Co-authors include Karla V. Ballman, Ph.D., of the Alliance Statistics and Data Center at Mayo Clinic in Rochester; Kelly K. Hunt, M.D., and Elizabeth A. Mittendorf, M.D., Ph.D., of MD Anderson Cancer Center; Linda M. McCall of the Alliance Statistics and Data Center at Duke University in Durham, N.C.; Gretchen M. Ahrendt, M.D., of the University of Pittsburgh Cancer Institute in Pittsburgh, Pa., and Lee G. Wilke, M.D., of the University of Wisconsin Hospital and Clinics in Madison, Wis.

http://www.eurekalert.org/pub_releases/2015-02/tjnj-ron012915.php

Review of nonmedicinal interventions for delirium in older patients

Multicomponent nonpharmacological delirium interventions showed significant reductions in the incidence of delirium

Interventions to prevent delirium that do not involve prescription drugs and have multiple components appeared to be effective at reducing delirium and preventing falls in hospitalized older patients, according to an article published online by JAMA Internal Medicine.

Delirium is a confused state that is marked by inattention and global cognitive dysfunction (impaired memory and thought). Delirium is common among hospitalized older patients and the condition increases the risk of falls, functional decline, dementia, prolonged hospital stays and institutionalization.

The Hospital Elder Life Program (HELP) is the original evidence-based approach to target delirium risk factors and it includes practical interventions such as reorientation, early mobilization, therapeutic activities, hydration, nutrition, strategies to improve sleep, and vision and hearing aids, according to background in the study.

Tammy T. Hshieh, M.D., of Brigham and Women's Hospital, Boston, and coauthors reviewed available medical literature and evaluated the evidence on multicomponent nonpharmacological delirium interventions. Their meta-analysis included 14 articles that involved 4,267 patients (average age nearly 80 years) at 12 sites (acute medical and surgical wards). The authors found that, overall, 11 studies showed significant reductions in the incidence of delirium and four randomized or matched clinical trials reduced delirium by 44 percent.

The rate of falls decreased among intervention patients in four studies, and in two randomized or matched trials the rate of falls was reduced by 64 percent. Length of hospital stay and institutionalization also trended toward decreases in intervention groups but the difference was not statistically significant, which the authors explained was not surprising given the multiple complex influences on these outcomes.

"In conclusion, this meta-analysis suggests that multicomponent nonpharmacological interventions are effective in decreasing delirium incidence and preventing falls, potentially saving more than $16 billion annually in the United States alone. Therefore, these strategies hold great promise to influence two of the most important and prevalent conditions affecting seniors during hospitalization.

Our systematic review and meta-analysis demonstrate that these interventions decrease the substantial health care and societal burden of delirium incidence and falls, improving quality of life for these patients and their families," the study concludes. (JAMA Intern Med. Published online February 2, 2015. doi:10.1001/jamainternmed.2014.7779. Available pre-embargo to the media at http://media.jamanetwork.com.)

Editor's Note: This study was supported in part by a grant from the National Institute on Aging. Authors also made funding/support disclosures. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.

Commentary: Delirium and the 'Know-Do' Gap in Acute Care for Older Patients

In a related commentary, S. Ryan Greysen, M.D., M.H.S., M.A., of the University of California, San Francisco, writes: "Numerous components of these interventions may simply seem too simple to question that they are not being done already. These include frequent orientation of patients to time, place and situation; early mobilization; attention to hearing and visual deficits and aids as appropriate; preservation of sleep-wake cycles; and adequate hydration. Indeed, it is quite likely that some of these interventions are occurring some of the time at many, if not most, hospitals, but the key to their effectiveness may well lie in the consistency of their application."

"Changing practice in the acute care setting is never easy and is often fraught with great uncertainty about risks and benefits to patients and the system. However, with respect to delirium prevention, the results by Hshieh et al suggest that it may no longer be a matter of evidence or knowing what to do. It may now be a matter of convincing hospitals and health care professionals to just do it," Greysen concludes.

(JAMA Intern Med. Published online February 2, 2015. doi:10.1001/jamainternmed.2014.7786. Available pre-embargo to the media at http://media.jamanetwork.com.)

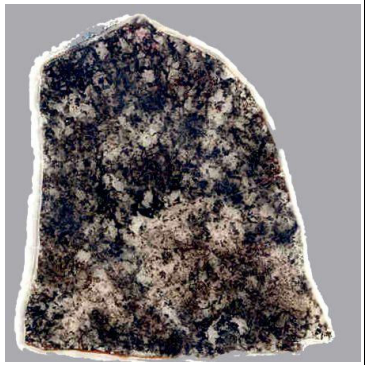
Editor's Note: Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, funding and support, etc.

http://www.eurekalert.org/pub_releases/2015-02/uoc - sdo020215.php

Scientists discover organism that hasn't evolved in more than 2 billion years

Research actually provides further support for Darwin, UCLA professor says

An international team of scientists has discovered the greatest absence of evolution ever reported - a type of deep-sea microorganism that appears not to have evolved over more than 2 billion years. But the researchers say that the organisms' lack of evolution actually supports Charles Darwin's theory of evolution. The findings are published online today by the Proceedings of the National Academy of Sciences.



This is a section of a 1.8 billion-year-old fossil-bearing rock. **UCLA Center for the Study of Evolution and the Origin of Life**

The scientists examined sulfur bacteria, microorganisms that are too small to see with the unaided eye, that are 1.8 billion years old and were preserved in rocks from Western Australia's coastal waters. Using cutting-edge technology, they found that the bacteria look the same as bacteria of the same region from 2.3 billion years ago - and that both sets of ancient bacteria are indistinguishable from modern sulfur bacteria found in mud off of the coast of Chile.

"It seems astounding that life has not evolved for more than 2 billion years - nearly half the history of the Earth," said J. William Schopf, a UCLA professor of earth, planetary and space sciences in the UCLA College who was the study's lead author. "Given that evolution is a fact, this lack of evolution needs to be explained."

Charles Darwin's writings on evolution focused much more on species that had changed over time than on those that hadn't. So how do scientists explain a species living for so long without evolving?

"The rule of biology is not to evolve unless the physical or biological environment changes, which is consistent with Darwin," said Schopf, who also is director of UCLA's Center for the Study of Evolution and the Origin of Life. The environment in which these microorganisms live has remained essentially unchanged for 3 billion years, he said.

"These microorganisms are well-adapted to their simple, very stable physical and biological environment," he said. "If they were in an environment that did not change but they nevertheless evolved, that would have shown that our understanding of Darwinian evolution was seriously flawed."

Schopf said the findings therefore provide further scientific proof for Darwin's work. "It fits perfectly with his ideas," he said.

The fossils Schopf analyzed date back to a substantial rise in Earth's oxygen levels known as the Great Oxidation Event, which scientists believe occurred between 2.2 billion and 2.4 billion years ago. The event also produced a dramatic increase in sulfate and nitrate - the only nutrients the microorganisms would have needed to survive in their seawater mud environment - which the scientists say enabled the bacteria to thrive and multiply.

Schopf used several techniques to analyze the fossils, including Raman spectroscopy - which enables scientists to look inside rocks to determine their composition and chemistry - and confocal laser scanning microscopy - which renders fossils in 3-D. He pioneered the use of both techniques for analyzing microscopic fossils preserved inside ancient rocks.

Co-authors of the PNAS research were Anatoliy Kudryavtsev, a senior scientist at UCLA's Center for the Study of Evolution and the Origin of Life, and scientists from the University of Wisconsin, NASA's Jet Propulsion Laboratory, Australia's University of New South Wales and Chile's Universidad de Concepción.

Schopf's research is funded by the NASA Astrobiology Institute.

http://bit.ly/1KuRCgl

These Dolphins Mourn Their Dead

A new study looks into a sad ritual at sea

By Erin Blakemore

Elephants feel empathy. Sea lions keen over the bodies of their loved ones. And new research suggests that yet another species mourns its dead: the spotted dolphin. Scientists have long observed dolphin rituals around death that suggest they don't like to leave their dead companions behind, reports Mary Bates for Wired. Now, a new study adds the Atlantic spotted dolphin to that list.

A group of Portuguese marine biologists studied two separate instances in which adult dolphins were recorded using their heads and backs to buoy up a calf who had recently died. Upon examining carcasses from those events and those of two other recently-dead calves, the biologists concluded that spotted dolphin adults tend to hold on to their dead young for about 30 minutes before giving them up to the ocean.

That's consistent with grieving, study lead Filipe Alves told Bates. He believes the behavior is tied to the complex generational connections that are common in ocean mammals:

Species that live in a matrilineal system, such as killer whales and elephants; species that live in pods of related individuals, such as pilot whales whose pods can comprise up to four generations of animals - when they spend a lifetime together, sometimes 60 years or more, yes, I believe they can grieve.

Alves and his colleagues stop short of using the word "grief" in their study, preferring to classify the dolphins' ritual as "nurturant behavior." The term covers a wide variety of animal activities such as social grooming, exchanging gifts, even adopting an animal from another species.

So do dolphins feel sad about their dead loved ones or not? While it's not certain which feelings drive the spotted dolphin's need to stay with its dead young, the ritual could be construed as mourning. And the existence of a post-mortem ritual is another item on a long list of things humans and dolphins share.

http://www.eurekalert.org/pub_releases/2015-02/tgso-drr020315.php

Dartmouth researchers reprogram tumor's cells to attack itself

Strain of bacteria inserted into the microenvironment of aggressive ovarian cancer transforms tumor cells from suppression to immunostimulation

Inserting a specific strain of bacteria into the microenvironment of aggressive ovarian cancer transforms the behavior of tumor cells from suppression to immunostimulation, researchers at Norris Cotton Cancer Center and the Geisel School of Medicine at Dartmouth have found. The findings, published in OncoImmunology, demonstrate a new approach in immunotherapy that can be applied in a variety of cancer types.

"By introducing an attenuated and safe form of the bacteria Listeria monocytogenes (Lm), in collaboration with Aduro Biotech Inc., we found that the attenuated bacteria is taken up by the immunosuppressive cells and transforms them from cells that protect the tumor into cells that attack the tumor," said Steve Fiering, PhD, lead author of the study.

Tumors protect themselves from attack by the immune system by generating an immunosuppressive microenvironment. The study's results found that Lm has a significant impact in increasing the amount of pro-inflammatory cytokines and chemokines, and recruiting immune effector cell subsets, that strongly support anti-tumor immunity. Modifying the immunosuppressive tumor microenvironment remains an approach that can be combined with other immune-based treatment to treat other cancers in addition to ovarian cancer.

"Modulation of the tumor microenvironment to make the immunosuppressive phagocytes into cells that support anti-tumor immune responses has roots in experiments done a hundred years ago by Dr. William Coley," Fiering said. "Now that we can engineer microorganisms to make them safe to use and also can track the anti-tumor immune response in great detail, it has new potential for use in cancer treatment."

The attenuated strain of Lm, developed by Aduro Biotech Inc., is already in clinical trials for the treatment of pancreatic cancer. "Our studies provide further understanding of the mechanisms involved and how this approach can be used in cancer treatment, and will support future clinical trials for treatment of ovarian cancer," Fiering said.

Co-authors on the study are Patrick H. Lizotte, BS, Jason R. Baird PhD, Cynthia A. Stevens MS, and William R. Green PhD of the Geisel School of Medicine at Dartmouth, and Peter Lauer PhD and Dirk G. Brockstedy Phd of Aduro Biotech, Inc. Funding was provided by Dartmouth Immunobiology of Myeloid and Lymphoid Cells NIH Training Grant 5T32AI007363-22 (P.H.L.); Dartmouth Center of Nanotechnology Excellence NIH 1 U54 CA151662 (S.F.); Center for Molecular, Cellular, and Translational Immunological Research NIGMS 1P30RR032136-01 (S.F.); Norris Cotton Cancer Support Grant P30 CA023108 (S.F.).Technical support was provided by Transgenic and Genetic Construct Shared Resource and by Dartlab Shared Resource with support from Norris Cotton Cancer Center.

http://www.eurekalert.org/pub_releases/2015-02/uog-tin020315.php

There is not a single type of schizophrenia, as thought, but 8 different genetic diseases

Researchers from the universities of Granada and Washington in St Louis break new ground in what could be an important first step towards better diagnosis and treatment of this disease

Scientists from the universities of Granada (Spain) and Washington in St Louis (US) have found that there is not a single type of schizophrenia, but that it consists of a group made up of eight genetically different types of diseases, each of which presents its own set of symptoms.

This important find, published recently by the prestigious American Journal of Psychiatry, could be an important first step towards a better diagnosis and treatment of this disease, which affects approximately 1% of world population.

It was known so far that approximately 80% of the risk of suffering from schizophrenia was hereditary, although scientists have struggled for years to identify which specific genes lead to it.

This new research, in which 4196 patients diagnosed with schizophrenia participated, has for the first time identified the different genes networks that contribute to the existence of eight different types of schizophrenia. In this research other 3200 healthy patients participated as control group.

Genes function as an orchestra

"Genes do not operate on their own, in an isolated manner", Igor Zwir, a researcher at the university of Granada and co-author of his article, pointed out, "they rather work with each other as an orchestra. To understand how they work, we must not just know what each member of this orchestra is like, but also how they interact with each other".

"What we did with this research, after a decade of frustration in the field of psychiatric genetics, is identify the manner in which the genes interact with each other, in an orchestrated manner in the case of healthy patients, or disorganized, as happens in the cases that lead to the different types of schizophrenia", claim the authors of the publication.

Thus, in some patients with hallucinations or delirium, for instance, researchers agree that there are different networks of genes related to their respective symptoms, which demonstrates that specific genetic variations interact with each other. This genetic analysis leads to 95% certainty in predicting the onset of schizophrenia. In another group, they found that incongruent speech and disorganized behaviour are specifically associated with a DNA variations network that leads to a 100% risk of suffering schizophrenia.

Researchers divided the patients according to the type and seriousness of positive symptoms (such as different types of hallucinations or deliriums), or negative symptoms (such as lack of initiative, troubles in organizing thoughts, or lack of connection between emotion and thought). In parallel, scientists classified the profiles of these symptoms into eight qualitative types of different diseases according to the underlying genetic conditions.

Individual genes

"In the past, scientists had searched for associations between individual genes and schizophrenia - researchers point out. What was lacking was the idea that these genes do not act independently, but that they work as a group instead, to disturb the structure and the functions of the brain, thus causing the disease."

Although individual genes only present weak, inconsistent associations with schizophrenia, the interaction networks of gene groups pose a high risk of suffering from the disease, between 70 and 100%, "which makes it almost impossible that individuals with those genetic variation networks will avoid schizophrenia"

Researchers found a total of 42 genes groups that influenced in a variety of ways the risk of suffering schizophrenia. They also replicated their finds in two independent samples of individuals with schizophrenia, an index that these networks are a valid path for the exploration and improvement of the diagnosis and treatment of this disease.

Profesor Zwir points out that, by identifying these genes networks and their adjustment within the symptoms in individual patients, 'it will soon be possible to determine a possible localized treatment for the specific paths that cause schizophrenia" and he emphasizes the fact that this work, published in the American Journal of Psychiatry, "has been performed and designed by researchers in the field of Computational Science".

http://www.eurekalert.org/pub_releases/2015-02/f-pp020315.php

'Cleaner' protein protects against atherosclerosis

A1M stops the oxidation of blood fats and keeps them in good condition

"Atherosclerosis is largely caused by oxidised blood fats. The research findings that we have presented in this paper show that A1M stops the oxidation of blood fats and keeps them in good condition. Not only that, A1M can also repair oxidised blood fats", said Professor Åkerström from the Faculty of Medicine at Lund University.

The protein A1M, alpha-1-microglobulin, exists in the body to clear out oxidised heme and other harmful molecules. Heme contains iron and is found in haemoglobin, which has the job of transporting oxygen around the body. When the oxygen is metabolised, harmful molecules known as free radicals are formed. The heme-molecule can also generate free radicals and release the toxic iron into our tissue, cells and DNA. The body has many methods of keeping both heme and free radicals in check.

Ten years ago Bo Åkerström and his research group demonstrated that A1M has the ability to bind the free radicals and the toxic heme molecules and convert them into harmless substances.

"You could say that the tissue is rinsed by A1M in a 5-10 minute cycle, with the protein absorbing the free radicals and heme-groups. A1M acts like a bin that captures and neutralises toxic substances throughout the body - in and around all cells - that would otherwise cause inflammation and damage to surrounding tissue", said Professor Åkerström.

In the present study, Bo Åkerström and his colleagues focused on two of the main causes of atherosclerosis: oxidation of LDL (commonly called 'bad cholesterol') and myeloperoxidase (MPO). MPO is a molecule in the white blood cells that is activated in inflammation and infection and, like haemoglobin, contains toxic heme substances.

"By studying and testing A1M's properties in relation to LDL and MPO, we discovered that A1M can clean and reduce oxidised blood fats from LDL, as well as taking care of the dangerous substances from MPO and breaking them down. "This means that A1M protects against damage to the molecules that we know is a cause of atherosclerosis", said Bo Åkerström.

The findings were obtained through lab research carried out in test tubes, but Bo Åkerström is hopeful:

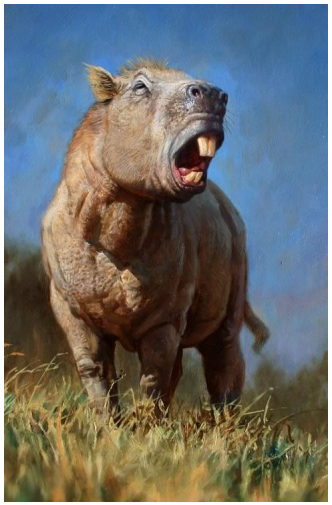
"The next step is animal experiments, as well as analysis of human tissues. We want to study the blood to see if there is a link between the level of A1M, the concentration of oxidised blood fats and the development of atherosclerosis.

"If this correlation exists, which I believe it does, I can imagine that it will be possible in the future to develop a preventive drug that reduces the risk of atherosclerosis. It's not impossible that future patients could receive one dose of A1M per month to clean the blood vessels."

http://www.eurekalert.org/pub_releases/2015-02/uoy-gru020315.php

Giant rodent used incisors like tusks

Largest rodent ever to have lived may have used its front teeth just like an elephant uses its tusks



The largest rodent ever to have lived may have used its front teeth just like an elephant uses its tusks, a new study led by scientists at the University of York and The Hull York Medical School (HYMS) has found.

Josephoartigasia monesi, a rodent closely related to guinea pigs, lived in South America approximately 3 million years ago. It is the largest fossil rodent ever found, with an estimated body mass of 1000 kg and was similar in size to a buffalo.

Dr Philip Cox, of the Centre for Anatomical and Human Sciences, a joint research centre of the University's Department of Archaeology and HYMS, used computer modelling to estimate how powerful the bite of Josephoartigasia could be.

A one-ton "fossil rat" has been discovered in South America, scientists announced today.

He found that, although the bite forces were very large - around 1400 N, similar to that of a tiger - the incisors would have been able to withstand almost three times that force, based on earlier estimates by co-authors, Dr Andres Rinderknecht, of The Museo Nacional de Historia Natural, Montevideo, and Dr Ernesto Blanco, of Facultad de Ciencias, Instituto de F?sica, Montevideo, who first described the fossil in 2008.

Dr Cox said: "We concluded that Josephoartigasia must have used its incisors for activities other than biting, such as digging in the ground for food, or defending itself from predators. This is very similar to how a modern day elephant uses its tusks."

The research, which is published in the Journal of Anatomy, involved CT scanning the Josephoartigasia monesi specimen and making a virtual reconstruction of its skull. This was then subjected to finite element analysis, an engineering technique that predicts stress and strain in a complex geometric object.

http://www.eurekalert.org/pub_releases/2015-02/sumc-sst012815.php

Stanford study ties immune cells to delayed onset of post-stroke dementia

A single stroke doubles a person's risk of developing dementia over the following decade, even when that person's mental ability is initially unaffected.

Why this delayed deterioration occurs has been a mystery. Now, Stanford University School of Medicine investigators think they have discovered a major reason for it.

In experiments using both mouse models of stroke and brain-tissue samples from humans, they linked the delayed onset of post-stroke dementia to the persistent presence, in the brain, of specialized immune cells that shouldn't be there at all. The discovery could potentially translate into ways of identifying people at risk for dementia, allowing physicians time to try to stave off the disease. Drugs that can disable these immune cells are already available.

At roughly 800,000 new cases per year, stroke is the second-biggest cause of serious long-term disability in the United States, generating $74 billion annually in treatment and caretaking costs. Of the 7 million living stroke survivors nationwide, one-third either suffers from dementia, or will.

In a study to be published Feb. 4 in The Journal of Neuroscience, a team directed by Marion Buckwalter, MD, PhD, assistant professor of neurosurgery and of neurology and neurosciences, examined several mouse models of stroke, as well as human brain-tissue samples, and found strong evidence that antibody-producing cells called B cells play a key role in the delayed onset of dementia. Buckwalter is the study's senior author. The lead author is former postdoctoral scholar Kristian Doyle, PhD.

B cells help, usually

The antibodies that B cells produce are normally of great value to us. They circulate throughout blood and lymph, and bind to microbial invaders, gumming up the pathogens' nefarious schemes and marking them for destruction by other immune cells. Occasionally, B cells wrongly begin generating antibodies that bind to the body's own healthy tissues, causing certain forms of autoimmune disease, such as rheumatoid arthritis. Rituxan, a drug approved by the Food and Drug Administration for this condition, is actually an antibody itself: Its target is a protein found on the surface of every B cell. Use of this drug depletes B cells in the body, relieving the symptoms of rheumatoid arthritis and other B-cell-mediated disorders.

Like almost all other types of immune cells, B cells are virtually nonexistent in the brains of healthy people, whose outermost ramparts are mostly impervious to

the cells and large molecules (like antibodies) freely circulating elsewhere. But the blood-brain barrier is not entirely unbreachable and is rendered much more permeable upon brain damage.

Two small reports from the last decade mentioned the puzzling presence of substantial numbers of immune cells in about 50 percent of the autopsied brains of people who had suffered strokes. This led Buckwalter to look more closely at the phenomenon.

Buckwalter is a team leader of Stanford's Stroke Collaborative Action Network, which is part of the Stanford Neurosciences Institute and coordinates stroke research efforts throughout the university. She was intrigued by those reports. So she and her colleagues embarked on a series of experiments in mouse models of stroke. Buckwalter's group fine-tuned their experimental procedures so that brain structures central to cognition in the mice would initially be left intact after a stroke.

"When we looked at the brains of these mice one week post-stroke, we saw a negligible presence of B cells in the stroke core," Buckwalter said. "But at seven weeks out, there were tons of them." The presence of B cells persisted at 12 weeks.

The cells tended to cluster in or near the stroke core, where normal brain cells that succumbed to stroke-induced oxygen deprivation had died. No such B-cell infiltration was evident in the brains of mice subjected to a sham procedure in which their brains experienced no stroke.

The scientists also determined that the B cells had been actively producing antibodies and progressing through various stages of development that typify such cells once they've been activated by exposure to foreign material.

Drug stems cognitive loss

In tests of the mice's ability to store short-term memory - a key yardstick in assessing dementia - mice in which a stroke had been induced performed about as well a week later as mice in the control group did, indicating that key brain structures in the post-stroke mice were as yet unharmed. But by seven weeks, the post-stroke mice had developed substantial memory deficits. Mice in the control group hadn't.

When Buckwalter and her associates performed their experiments on post-stroke mice that were genetically altered to be incapable of generating B cells, they suffered no such delayed cognitive impairment.

So the investigators repeated their set of experiments on the same normal laboratory mice strain they'd previously been working with - except that this time, beginning five days after stroke was induced and continuing biweekly for several weeks, the mice were given a mouse analog of Rituxan to deplete their B cells. This time, the post-stroke mice exhibited no signs of delayed cognitive loss.

Finally, the Stanford scientists examined autopsied brain sections from stroke cores of 21 stroke patients, all of whom had dementia. Among these, 12 contained suspiciously high numbers of B cells.

To see if a prominent B-cell presence in the brain might be a common occurrence in old age, even among healthy people, they looked at brain samples from nine age-matched patients with no history of stroke or dementia. In these brains, B cells were rare.

More work needed for a therapy

Buckwalter speculated that B cells entering a brain rendered accessible by a stroke may, upon exposure to intercellular substances released by dead or dying cells, become reactive to brain tissue, setting off a spiraling cycle of spreading cell injury and further B-cell activation. It's likely that this happens in only a fraction, albeit possibly a substantial one, of stroke patients, she cautioned, so it would be medically unsound to simply dose all stroke patients with a B-cell-depleting drug. But she suggested that a brain-penetrating, B-cell-tagging compound or antibody that was labeled for detection by, say, MRI could help identify candidates for such a therapy.

"We're not there yet. Much more work needs to be done to nail down who this happens to and what's the right drug timing and dosage," Buckwalter said. "But it's exciting to think that delayed-onset post-stroke dementia, which carries such an enormous cost to individuals and to society, is potentially treatable."

The study was supported by the National Institutes of Health (grants R01NS067132 and K99NR012593). Other Stanford co-authors are neurology professor Lawrence Steinman, MD; Frank Longo, MD, PhD, professor and chair of neurology; visiting scholar Montse Sole, PhD; research associate Thuy-Vi Nguyen, PhD; postdoctoral scholars Robert Axtell, PhD, Gilberto Soler-Llavia, PhD, and Sandra Jurado, PhD; and life science research assistants Jullet Han and Lisa Quach.

http://www.eurekalert.org/pub_releases/2015-02/nu-sby020315.php

Superager brains yield new clues to their remarkable memories

Brains of cognitively elite look distinctly different than their elderly peers

CHICAGO - SuperAgers, aged 80 and above, have distinctly different looking brains than those of normal older people, according to new Northwestern Medicine® research that is beginning to reveal why the memories of these cognitively elite elders don't suffer the usual ravages of time.

SuperAgers have memories that are as sharp as those of healthy persons decades younger.

Understanding their unique "brain signature" will enable scientists to decipher the genetic or molecular source and may foster the development of strategies to protect the memories of normal aging persons as well as treat dementia.

Published Jan. 28 in the Journal of Neuroscience, the study is the first to quantify brain differences of SuperAgers and normal older people.

Cognitive SuperAgers were first identified in 2007 by scientists at Northwestern's Cognitive Neurology and Alzheimer's Disease Center at Northwestern University Feinberg School of Medicine.

Their unusual brain signature has three common components when compared with normal persons of similar ages: a thicker region of the cortex; significantly fewer tangles (a primary marker of Alzheimer's disease) and a whopping supply of a specific neuron - von Economo - linked to higher social intelligence.

"The brains of the SuperAgers are either wired differently or have structural differences when compared to normal individuals of the same age," said Changiz Geula, study senior author and a research professor at the Cognitive Neurology and Alzheimer's Disease Center. "It may be one factor, such as expression of a specific gene, or a combination of factors that offers protection."

The Center has a new NIH grant to continue the research.

"Identifying the factors that contribute to the SuperAgers' unusual memory capacity may allow us to offer strategies to help the growing population of 'normal' elderly maintain their cognitive function and guide future therapies to treat certain dementias," said Tamar Gefen, the first study author and a clinical neuropsychology doctoral candidate at Feinberg.

MRI imaging and an analysis of the SuperAger brains after death show the following brain signature:

1) MRI imaging showed the anterior cingulate cortex of SuperAgers (31 subjects) was not only significantly thicker than the same area in aged individuals with normal cognitive performance (21 subjects), but also larger than the same area in a group of much younger, middle-aged individuals (ages 50 to 60, 18 subjects). This region is indirectly related to memory through its influence on related functions such as cognitive control, executive function, conflict resolution, motivation and perseverance.

2) Analysis of the brains of five SuperAgers showed the anterior cingulate cortex had approximately 87 percent less tangles than age-matched controls and 92 percent less tangles than individuals with mild cognitive impairment. The neurofibrillary brain tangles, twisted fibers consisting of the protein tau, strangle and eventually kill neurons.

3) The number of von Economo neurons was approximately three to five times higher in the anterior cingulate of SuperAgers compared with age-matched controls and individuals with mild cognitive impairment.

"It's thought that these von Economo neurons play a critical role in the rapid transmission of behaviorally relevant information related to social interactions," Geula said, "which is how they may relate to better memory capacity." These cells are present in such species as whales, elephants, dolphins and higher apes.

Other Northwestern authors on the study include Melanie Peterson, Steven T. Papastefan, Adam Martersteck, Kristen Whitney, Alfred Rademaker, Eileen Bigio, Sandra Weintraub, Emily Rogalski and Dr. M. Marsel Mesulam.

The research was funded by National Institute on Aging, National Institutes of Health grant AG045571, The Davee Foundation, the Northwestern University Alzheimer's Disease Core Center grant AG13854 from the National Institute on Aging, a fellowship from the National Institute on Aging grant F31-AG043270 and others.

For more information on the SuperAger study, visit http://www.brain.northwestern.edu.

If you are interested in participating in research at Northwestern University, please call the NU Study line at 1-855-NU-STUDY. Or get connected by visiting http://bit.ly/NUCATSRegistry to sign up for Northwestern's Research Registry.

NORTHWESTERN NEWS: http://www.northwestern.edu/newscenter/

http://bit.ly/1vvJ87A

Green light for mission to Jupiter moon Europa

Pack your ice gear – we're going to Europa.

- **12:58 03 February 2015 by Lisa Grossman**

NASA's budget request for 2016 includes $30 million for a dedicated mission to Jupiter's icy moon, which is considered one of the best prospects for discovering life in our solar system.

Europa has been a tempting destination for planetary scientists since the mid-1990s, when the Galileo orbiter revealed that it may harbour a deep ocean of briny liquid water beneath a thick icy shell. More recently, reports that plumes of subsurface water could be venting into space sparked calls for a mission to sample that water directly and see if anything lives in it.

Last year, NASA received $100 million from Congress to begin preliminary work on such a mission, but was missing the commitment to further funding for a period long enough to plan a mission.

Now, with another $255 million budgeted over the next 5 years, NASA is giving a clearer green light. "For the first time, the budget supports the formulation and development of a Europa Mission, allowing NASA to begin project formulation," the budget request reads.

The mission will probably involve a spacecraft orbiting Jupiter and making multiple fly-bys of Europa, rather than landing on or orbiting Europa itself. This will make the mission much cheaper and safer, as Europa sits in a harsh radiation environment that can be dangerous for spacecraft. NASA will choose instruments for the spacecraft in spring this year, and aims for a launch date in the mid-2020s.

"This is a big deal," says Robert Pappalardo at NASA's Jet Propulsion Lab in Pasadena, California, the pre-project scientist for the Europa Clipper probe concept. "We're moving toward the next phase, where you're a real mission. It's just thrilling after 15 years of pushing for it. It's a great day."

http://nyti.ms/1FdLqIB

Scientists Discover "Reset" Button for Circadian Rhythm

Could a simple reboot turn exhaustion into a thing of the past?

By Erin Blakemore

Our circadian rhythms rule our lives, regulate our sleep and tell us when to get up in the morning. But though scientists know how critical our internal clocks are to health and human performance, they haven't been able to predictably control them. That could be about to change. At Vanderbilt University, biologists have figured out how to stimulate and manipulate the neurons that control the circadian rhythms of mice.

The rodents may be nocturnal, but otherwise their biological clocks are nearly identical to those of humans.

The study hinges on a part of the brain called the suprachiasmatic nucleus (SCN), home to the body's master clock.

Scientists used to think that more activity in the SCN meant that they'd see more neurons firing - that the firing rate of neurons was an output of the clock's natural activity. But the research team from Vanderbilt learned that they had it all backwards, when they inserted genes into the neurons of mice to make those cells respond to light.

In the experiment, one group of mice had neurons that would fire more often when exposed to light; another had neurons that would fire more often when light was suppressed.

That meant the researchers were able to control the neurons' firing rate, and they were able to show that by manipulating the firing rate, they could actually *stimulate* the SCN.

"This suggests that SCN firing rate is fundamental to circadian pacemaking as both an input to and output of the molecular clockworks," they write in their paper.

In other words, triggering or suppressing the right neurons effectively reset the SCN, rebooting the biological clock.

"This puts clock neurons under our control for the first time," said Jeff Jones, a doctoral student who co-conducted the study, in a release.

The team hopes that this strategy - causing cells to respond to light - could be the key to a cure for jet lag, seasonal affective disorder or the clock confusion caused by shift work.

Given last week's announcement that a new pill could help fool the body into thinking it's a different time of day, it could be a mere matter of time until a genetic modification or a prescription helps us feel less sleepy. But hold on to your coffee cup - it could be years before optogenetics hit the medical mainstream.

http://www.eurekalert.org/pub_releases/2015-02/bmj-rga020315.php

Recent gut and urinary tract infections may curb risk of rheumatoid arthritis

Recent gut and urinary tract infections may curb the risk of developing rheumatoid arthritis, suggests research published online in the Annals of the Rheumatic Diseases.

One possible explanation could lie in the way in which these infections alter the types of bacteria resident in the gut (microbiome), say the researchers.

They set out to look at the impact of different types of infection on the risk of developing rheumatoid arthritis in almost 6500 people living in south and central Sweden. Some 2831 of the entire sample had been newly diagnosed with rheumatoid arthritis between 1996 and 2009. The remaining 3570, who were randomly selected from the population, were healthy, but matched for age, sex, and area of residence with the patients.

All participants were asked whether they had had any gut, urinary tract, or genital infections in the preceding two years. They were also asked if they had had prostatitis (inflamed prostate), or antibiotic treatment for sinusitis, tonsillitis/other throat infection, or pneumonia during this time. The average age of all participants at study entry was 52, and 7 out of 10 of them were women.

Gut, urinary tract, and genital infections within the preceding two years were each associated with a significantly lowered risk of developing rheumatoid arthritis: by 29%, 22%, and 20%, respectively. And having all three types of infection in the preceding two years was linked to a 50% lower risk, after taking account of influential factors. By contrast, no such associations were found for recent respiratory infections and pneumonia. Factoring in smoking and socioeconomic background made no difference to the overall findings.

More recent infection within the past year did not affect rheumatoid arthritis risk, but the impact of gut, urinary tract, and genital infections within the past two years seemed to be stronger in those who had tested positive for a particular type of protein associated with subsequent development of rheumatoid arthritis (ACPA).

This is an observational study so no definitive conclusions can be drawn about cause and effect. But the researchers say their findings "are particularly interesting in light of emerging data implicating that the microbiome in the gut may play a role in rheumatoid arthritis pathogenesis."

This might be because the linings of the gut are exposed to a high load of bacterial antigens, which may either initiate or modify inflammation, and so could possibly influence the risk of developing the disease, explain the researchers.

In support of their findings, they point out that the infection sites identified in their study are primarily infected with gram negative bacteria, and antibiotics used to treat these bacteria have proved effective for treating rheumatoid arthritis.

http://www.eurekalert.org/pub_releases/2015-02/uoc - pmb020215.php

Paramedics may be first source of treatment for stroke patients, UCLA study finds

Working with paramedics allows IV medications to be administered within 'golden hour'

In the first study of its kind, a consortium led by UCLA physicians found that paramedics can start medications for patients in the first minutes after onset of a stroke. While the specific drug tested, magnesium sulfate, did not improve patient outcomes, the research has resulted in a new method to get promising treatments to stroke patients quickly.

The study found that, by working with paramedics in the field, intravenous medications can be given to stroke patients within the "golden hour," the window in which patients have the best chance to survive and avoid debilitating, long-term neurological damage. That finding is a "game changer," said study co-principal investigator Dr. Jeffrey Saver, director of the UCLA Stroke Center and professor of neurology at the David Geffen School of Medicine at UCLA.

"The trial succeeded in its goal of devising a means to deliver promising drugs to stroke patients in the first minutes, when there's the greatest amount of brain to save. We have opened a new therapeutic window that is now being used to test other compounds and deliver clot-busting drugs to patients in the field," Saver said. "Stroke is a true emergency condition. Time lost is brain lost - for every minute that goes by without restoration of blood flow, two million nerve cells are lost. If these patients don't get protective drugs until two, three or four hours later, irreversible brain damage will have already occurred." The study appears in the Feb. 5, 2015 issue of the peer-reviewed New England Journal of Medicine.

The Phase III Field Administration of Stroke Therapy - Magnesium (FAST-MAG) clinical trial involved collaboration between 315 ambulances, 40 emergency medical service agencies, 60 receiving hospitals, 715 emergency physicians, 210 neurologists, 26 neurosurgeons and 2,988 paramedics. The study demonstrated that half of the 1,700 patients in Los Angeles and Orange counties had the study drug administered within 45 minutes, while 74 percent were treated within the first "golden hour."

"This study involved an unprecedented cooperative effort of paramedics in the field and emergency physicians serving as investigators," said co-principal investigator Dr. Sidney Starkman, co-director of the UCLA Stroke Center and professor of emergency medicine and neurology at the David Geffen School of Medicine at UCLA. "What they did was really quite heroic, and through this study we were able to instill permanently in everyone's mind the idea that 'time is brain.' We believe this represents a paradigm shift in the treatment of stroke and potentially numerous other neurological conditions."

Starkman reiterated that the study would not have been possible without the approval and confidence of the California and local emergency medical service agencies and the administrations of the participating hospitals.

"Never before have so many emergency physicians, neurologists, neurosurgeons, nurses and such a large number of paramedics worked together in a National Institutes of Health study. Rapidly and without transport delay, we identified patients who were having a stroke with 96 percent accuracy," Starkman said. "We demonstrated that paramedics not only are eager to provide the best possible patient care, but also are capable of being invaluable partners in an intense, time-dependent clinical trial."

Today, the only treatments for strokes caused by blockage of blood vessels are reopening the arteries with the clot-busting drug tissue plasminogen activator (tPA) or with catheter devices that physically remove the clot. Typically, these treatments cannot be used until the patients arrive at the hospital and undergo a CT scan to rule out bleeding in the brain. Only afterwards can additional treatments be offered. By the time these treatments are started, substantial brain injury has often already occurred.

For the FAST-MAG trial, magnesium was chosen because it dilated blood vessels in the brain in animal studies, increasing blood flow. It also countered the damaging calcium build up that occurs in cells deprived of oxygen. It had been already approved to treat medical conditions in people, was known to have a good safety profile and paramedics were familiar with it.

"Now we are tasked with finding a different agent or combination of agents that can improve stroke outcomes within that golden hour," Saver said. "The ambulance treatment platform can be used around the world to test promising agents. FAST-MAG has opened a new, earlier-than-ever window for treatment that has the potential to significantly improve outcomes for the hundreds of thousands of people each year who suffer a stroke."

Dr. Bill Koenig, medical director of the Los Angeles County Emergency Medical Service (EMS) agency, worked closely with Saver and Starkman on the FAST-MAG study. He said the benefits of the agency's participation in the FAST-MAG trial "cannot be overstated."

"To assist paramedic recognition of stroke victims, the nationally recognized Los Angeles Pre-hospital Stroke Screen was developed. FAST-MAG also served as an

impetus to create the Los Angeles County System of Stroke Hospitals, which every year treats over 10,000 stroke victims," Koenig said. "When the day comes that a medication can successfully treat stroke in its early stages, this novel system in Los Angeles will be well positioned to immediately apply the treatment to our patients. I am confident that with the dedicated investigators, along with a finely tuned EMS system, that discovery will be sooner rather than later."

Dr. Walter Koroshetz, acting director of the National Institute of Neurological Disorders and Stroke, said this study "shows that it is possible to get treatments to stroke patients even before they arrive at a hospital."

"Because a blocked blood vessel causes brain damage over minutes to hours, this pre-hospital approach to treatment is sure to be adopted and refined in clinical research studies," Koroshetz said. "Ultra-early brain salvage in stroke patients will someday surely reduce the tremendous burden of disability and death due to stroke."

Saver said there are currently clinical trials being conducted in United States, Canada and England testing new compounds using the early treatment infrastructure created by the FAST-MAG study.

Stroke is the fifth leading cause of death in the United States and is a major cause of adult disability. About 800,000 people in the United States have a stroke each year. One American dies from a stroke every four minutes, on average.

The study was funded by the National Institutes of Neurological Disorders and Stroke at the National Institutes of Health.

http://www.eurekalert.org/pub_releases/2015-02/ps-dgt020415.php

Drinking green tea before taking supplements may offer protection from toxicity

As high doses of green tea extract supplements for weight loss become more popular, potential liver toxicity becomes a concern.

In the last decade, dozens of people have been diagnosed with the condition. However, drinking green tea in the weeks before taking supplements likely reduces risk, according to researchers in Penn State's College of Agricultural Sciences.

Researchers gave mice high doses of the green tea polyphenol epigallocatechin-3-gallate (EGCG). The dosage was equivalent to the amount of the polyphenol found in some dietary supplements taken by humans.

One group of mice was pretreated with a diet containing a low level of EGCG for two weeks prior to receiving high doses of the polyphenol. Another group was fed a diet that did not include EGCG prior to receiving the high, supplement-like doses. After three days of high doses, the scientists tested the blood of the mice to determine how their livers handled the EGCG. Pretreated mice had a 75 percent reduction in liver toxicity compared to untreated mice.

The research data show that dietary pretreatment with the green tea polyphenol protects mice from liver toxicity caused by subsequent high oral doses of the same compound, explained Josh Lambert, associate professor of food science. He suggested that the research has relevance to people who are taking or are considering taking supplements containing green tea extract.

"We believe this study indicates that those who are chronic green tea consumers would be less sensitive to potential liver toxicity from green-tea-based dietary supplements," he said. "If you are going to take green tea supplements, drinking green tea for several weeks or months ahead of time may reduce your potential side effects."

Lambert has another suggestion for people considering green tea supplements - drink green tea instead. "Drinking green tea rather than taking supplements will allow you to realize the benefits and avoid the risk of liver toxicity," he said. "The beneficial effects that people have reported as being associated with green tea are the result of dietary consumption rather than the use of supplements. The relative risk of using supplements remains unclear."

Tea - Camellia sinensis - is rich in catechins, polyphenols that are natural antioxidants. A number of animal studies have shown the preventive effects of green tea polyphenols against obesity. And Lambert pointed out that a recent analysis of 11 human trials with green tea preparations reported a nearly three-pound average body weight loss in intervention groups compared to control groups.

Green tea's effect on weight loss may be more noticeable if a person exercises. In research published last year, Lambert showed that mice on a high-fat diet that consumed decaffeinated green tea extract and exercised regularly experienced sharp reductions in final body weight and significant improvements in health.

Approximately 34 percent of adults in the United States are classified as obese, Lambert noted, leading to a strong interest in the potential benefits of including green tea and green tea supplements in weight-loss efforts. The liver toxicity research, recently published online in Food and Chemical Toxicology, revealed a unique property of the green tea polyphenol EGCG.

"It appears that EGCG can modulate its own bioavailability and that dietary treatment may reduce the toxic potential of acute high oral doses of EGCG," said lead researcher Sarah Forester, assistant professor of chemistry, California State University, Bakersfield, a former Penn State postdoctoral fellow.

"These data may partly explain the observed variation in liver toxicity response to dietary supplements containing green tea."

Some people drink surprisingly large volumes of green tea, according to Lambert, as much as 10-20 cups a day, but liver toxicity has never been reported in that context.

"No person can sit down and drink 16 cups of green tea all at once," he said. "However if you take a supplement you can get that type of green tea extract dose, so there is some indication that the dosage form has an influence on the potential to cause liver toxicity."

http://www.eurekalert.org/pub_releases/2015-02/idso-rau020415.php

Rapid and unexpected weight gain after fecal transplant

Patient treated successfully for* Clostridium difficile *infection with stool from overweight donor rapidly gained weight herself afterwards

A woman successfully treated for a recurrent *Clostridium difficile* infection with stool from an overweight donor rapidly gained weight herself afterwards, becoming obese, according to a case report published in the new journal *Open Forum Infectious Diseases*.

Fecal microbiota transplant (FMT) is a promising treatment for relapsing *C. difficile* infections, a common cause of antibiotic-related diarrhea that in severe cases may be life-threatening. The case suggests that clinicians should avoid selecting stool donors who are overweight. The report also raises questions about the role of gut bacteria in metabolism and health.

At the time of the woman's fecal transplant in 2011, her weight was stable at 136 pounds, and her Body Mass Index (BMI) was 26. Then 32 years old, she had always been of normal weight. The transplant used donor stool from the woman's overweight but otherwise healthy teenage daughter, administered via colonoscopy, to restore a healthy balance of bacteria in the woman's gut, curing her *C. difficile* infection.

Sixteen months later, the woman weighed 170 pounds, and her BMI was 33, meeting medical criteria for obesity. The weight gain persisted despite a medically supervised liquid protein diet and exercise program. Continuing efforts to diet and exercise did not lower her weight: Three years after the transplant, she weighed 177 pounds with a BMI of 34.5, and she remains obese today.

"We're questioning whether there was something in the fecal transplant, whether some of those 'good' bacteria we transferred may have had an impact on her metabolism in a negative way," said Colleen R. Kelly, MD, of the Warren Alpert Medical School of Brown University, who wrote the case report with Neha Alang, MD, of Newport Hospital in Rhode Island. Such a link between bacteria in the gastrointestinal tract and weight is supported by previously published animal studies, where transfer of gut bacteria from obese to normal-weight mice can lead to a marked increase in fat. In light of the case and the animal data, the authors recommend selecting stool donors who are not overweight for fecal transplants.

Importantly, the FMT was not the only possible cause of the woman's weight gain. In addition to treatment for *C. difficile*, she had also been treated with several antibiotics for Helicobacter pylori infection. Other possible contributing factors in the woman's weight gain include the resolution of her *C. difficile* infection, genetic factors, aging, and stress related to illness. However, as noted above, she had never been overweight before.

The case raises many questions about donor selection and highlights the importance of studying long-term outcomes of FMT, according to Ana A. Weil, MD, and Elizabeth L. Hohmann, MD, both of Massachusetts General Hospital, who wrote a related editorial.

"Careful study of FMT will advance knowledge about safe manipulation of the gut microbiota," they wrote. "Ultimately, of course, it is hoped that FMT studies will lead to identification of defined mixtures of beneficial bacteria that can be cultured, manufactured, and administered to improve human health."

Fast Facts

- ***Fecal transplants are a promising approach for treating recurrent C. difficile infections, a common cause of potentially life-threatening diarrhea.***
- ***In this case report, a woman successfully treated for a relapsing C. difficile infection with a fecal transplant rapidly became overweight for the first time in her life. The stool donor, the woman's daughter, was overweight.***
- ***The report suggests that donor screening for these transplants should exclude those who are overweight.***

The case report and editorial are available online:Weight Gain After Fecal Microbiota Transplantation http://ofid.oxfordjournals.org/content/2/1/ofv004.full

Fecal Microbiota Transplant: Benefits and Risks
http://ofid.oxfordjournals.org/content/2/1/ofv005.full

http://www.eurekalert.org/pub_releases/2015-02/uoi-pp020415.php

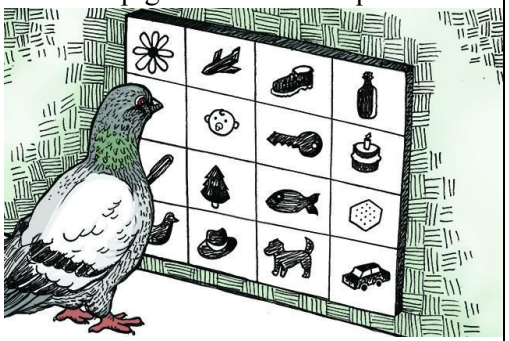
Pigeon power

New UI study suggests similarity between how pigeons learn the equivalent of words and the way children do

The more scientists study pigeons, the more they learn how their brains - no bigger than the tip of an index finger - operate in ways not so different from our own.

In a new study from the University of Iowa, researchers found that pigeons can categorize and name both natural and manmade objects - and not just a few objects. These birds categorized 128 photographs into 16 categories, and they did so simultaneously.

Ed Wasserman, UI professor of psychology and corresponding author of the study, says the finding suggests a similarity between how pigeons learn the equivalent of words and the way children do.



"Unlike prior attempts to teach words to primates, dogs, and parrots, we used neither elaborate shaping methods nor social cues," Wasserman says of the study, published online in the journal Cognition. "And our pigeons were trained on all 16 categories simultaneously, a much closer analog of how children learn words and categories."

In a new study from the University of Iowa, researchers found that pigeons can categorize and name both natural and manmade objects - and not just a few objects. These birds categorized 128 photographs into 16 categories, and they did so simultaneously. **Illustration by John Petsel (B.F.A. '15 in graphic design).**

For researchers like Wasserman, who has been studying animal intelligence for decades, this latest experiment is further proof that animals - whether primates, birds, or dogs - are smarter than once presumed and have more to teach scientists.

"It is certainly no simple task to investigate animal cognition; But, as our methods have improved, so too have our understanding and appreciation of animal intelligence," he says. "Differences between humans and animals must indeed exist: many are already known. But, they may be outnumbered by similarities. Our research on categorization in pigeons suggests that those similarities may even extend to how children learn words."

Wasserman says the pigeon experiment comes from a project published in 1988 and featured in The New York Times in which UI researchers discovered pigeons could distinguish among four categories of objects.

This time, the UI researchers used a computerized version of the "name game" in which three pigeons were shown 128 black-and-white photos of objects from 16 basic categories: baby, bottle, cake, car, cracker, dog, duck, fish, flower, hat, key, pen, phone, plan, shoe, tree. They then had to peck on one of two different symbols: the correct one for that photo and an incorrect one that was randomly chosen from one of the remaining 15 categories. The pigeons not only succeeded in learning the task, but they reliably transferred the learning to four new photos from each of the 16 categories.

Pigeons have long been known to be smarter than your average bird - or many other animals, for that matter. Among their many talents, pigeons have a "homing instinct" that helps them find their way home from hundreds of miles away, even when blindfolded. They have better eyesight than humans and have been trained by the U. S. Coast Guard to spot orange life jackets of people lost at sea. They carried messages for the U.S. Army during World Wars I and II, saving lives and providing vital strategic information.

UI researchers say their expanded experiment represents the first purely associative animal model that captures an essential ingredient of word learning - the many-to-many mapping between stimuli and responses.

"Ours is a computerized task that can be provided to any animal, it doesn't have to be pigeons," says UI psychologist Bob McMurray, another author of the study. "These methods can be used with any type of animal that can interact with a computer screen." McMurray says the research shows the mechanisms by which children learn words might not be unique to humans.

"Children are confronted with an immense task of learning thousands of words without a lot of background knowledge to go on," he says. "For a long time, people thought that such learning is special to humans. What this research shows is that the mechanisms by which children solve this huge problem may be mechanisms that are shared with many species."

Wasserman acknowledges the recent pigeon study is not a direct analogue of word learning in children and more work needs to be done. Nonetheless, the model used in the study could lead to a better understanding of the associative principles involved in children's word learning.

"That's the parallel that we're pursuing," he says, "but a single project - however innovative it may be - will not suffice to answer such a provocative question."

National Institute of Mental Health Grant MH47313, National Eye Institute Grant EY019781, and National Institute of Deafness and Other Communication Disorders Grant DC0008089 supported the research.

http://www.eurekalert.org/pub_releases/2015-02/anu-spe020415.php

Scientists predict earth-like planets around most stars

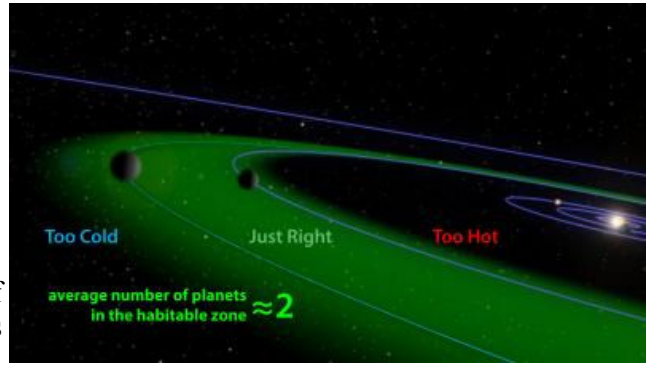
Planetary scientists have calculated that there are hundreds of billions of Earth-like planets in our galaxy which might support life, by applying a 200 year old idea to the thousands of exoplanets discovered by the Kepler space telescope.

Planetary scientists have calculated that there are hundreds of billions of Earth-like planets in our galaxy which might support life.

The new research, led by PhD student Tim Bovaird and Associate Professor Charley Lineweaver from The Australian National University (ANU), made the finding by applying a 200 year old idea to the thousands of exo-planets discovered by the Kepler space telescope.

They found the standard star has about two planets in the so-called goldilocks zone, the distance from the star where liquid water, crucial for life, can exist.

"The ingredients for life are plentiful, and we now know that habitable environments are plentiful," said Associate Professor Lineweaver, from the ANU Research School of Astronomy and Astrophysics and the Research School of Earth Sciences.



This is the Goldilocks zone, where liquid water can exist. **Aditya Chopra, ANU, adapted from NASA/JPL**

"However, the universe is not teeming with aliens with human-like intelligence that can build radio telescopes and space ships. Otherwise we would have seen or heard from them.

"It could be that there is some other bottleneck for the emergence of life that we haven't worked out yet. Or intelligent civilisations evolve, but then self-destruct."

The Kepler space telescope is biased towards seeing planets very close to their stars, that are too hot for liquid water, but the team extrapolated from Kepler's results using the theory that was used to predict the existence of Uranus.

"We used the Titius-Bode relation and Kepler data to predict the positions of planets that Kepler is unable to see," Associate Professor Lineweaver said.

http://www.eurekalert.org/pub_releases/2015-02/uor-aep020415.php

An extra protein gives naked mole rats more power to stop cancer

A protein newly found in the naked mole rat may help explain its unique ability to ward off cancer.

The protein is associated with a cluster of genes (called a locus) that is also found in humans and mice. It's the job of that locus to encode - or carry the genetic instructions for synthesizing - several cancer-fighting proteins. As Professor of Biology Vera Gorbunova explains, the locus found in naked mole rats encodes a total of four cancer-fighting proteins, while the human and mouse version encodes only three proteins. The findings by Gorbunova, Assistant Professor of Biology Andrei Seluanov, and their research team have been published in the Proceedings of the National Academy of Sciences.

It had already been known that the genes in question - referred to as INK4 gene locus - synthesize the same three cancer-suppressing proteins in both species: p15INK4b, p16INK4a, and ARF, all of which stop cells from dividing when the cells are stressed or mutated. A student-researcher, Jorge Azpurua, wanted to clone the p16 protein of the naked mole rat for a separate experiment and noticed something unexpected: The presence of a fourth protein, which was the result of p15INK4b and p16INK4a being fused together. This fourth protein was as good or even better than p15INK4b and p16INK4a at stopping cells from dividing.

"We named this novel product pALTINK4a/b," said Gorbunova, "and we believe it may contribute to the longevity of the naked mole rat, including its ability to prevent tumors from developing."

Naked mole rats are small, hairless, subterranean rodents that have never been known to get cancer despite having a 30-year lifespan.

Previous research by Seluanov and Gorbunova identified HMW-HA as the chemical that activates the anti-cancer response of the INK4 locus.

"INK4 is the most commonly mutated gene locus in the human cancer," said Seluanov. "When that gene is deleted or silenced, it often results in the formation of tumors." And, as he pointed out, there is growing evidence to support its role in atherosclerosis and other aging-related diseases.

"Considering how mutations in the INK4 gene are linked to human cancers," said Gorbunova, "the better we understand that gene and control its mutations, the better our chances of controlling some cancers."

In order to determine the significance of pALTINK4a/b, the researchers examined the expression of the proteins under different cell growth conditions. They found that the presence of the hybrid protein does increase when cells become crowded, as long as HMW-HA is present. On the other hand, when HMW-HA was removed, pALTINK4a/b was not expressed, but it was also induced by a variety of stresses such as oncogenes, which have the potential to cause cancer. The researchers concluded that the protein does respond to high-cell density and to HMW-HA, which initiates the anti-cancer response of the INK4 gene. The presence of the fourth INK4 protein, pALTINK4a/b, makes naked mole rats more likely to arrest growth when there is a risk of malignancy, compared to other mammals that have only three proteins encoded by INK4 locus.

In an effort to determine whether pALTINK4a/b is also found in mice and humans, the researchers tried to screen mouse and human cells and tissues for the protein hybrid, but were unsuccessful. "While our work doesn't eliminate the possibility that the protein exists under some conditions in mice and humans, the results suggest that it's highly unlikely," said Gorbunova.

The research team also included Adeline Augereau and Vadim Gladyshev of Brigham and Women's Hospital at Harvard University, Zhengdong Zhang and Jan Vijg of Albert Einstein College of Medicine, and Jorge Azpurua and Zonghe Ke of the University of Rochester.

http://bit.ly/1AAne4n

Blood Type Matters for Brain Health

People with AB blood type are at higher risk for age-related cognitive decline

Dec 18, 2014 |By Andrea Anderson and Victoria Stern

Blood type may affect brain function as we age, according to a new large, long-term study. People with the rare AB blood type, present in less than 10 percent of the population, have a higher than usual risk of cognitive problems as they age.

University of Vermont hematologist Mary Cushman and her colleagues used data from a national study called REGARDS, which has been following 30,239 African-American and Caucasian individuals older than 45 since 2007. The aim of the study is to understand the heavy stroke toll seen in the southeastern U.S., particularly among African-Americans. Cushman's team focused on information collected twice yearly via phone surveys that evaluate cognitive skills such as learning, short-term memory and executive function. The researchers zeroed in on 495 individuals who showed significant declines on at least two of the three phone survey tests.

When they compared that cognitively declining group with 587 participants whose mental muster remained robust, researchers found that impairment in thinking was roughly 82 percent more likely in individuals with AB blood type than in those with A, B or O blood types, even after taking their race, sex and geography into account. The finding was published online last September in *Neurology*.

The seemingly surprising result has some precedent: past studies suggest non-O blood types are linked to elevated incidence of heart disease, stroke and blood clots - vascular conditions that could affect brain function. Yet these cardiovascular consequences are believed to be linked to the way non-O blood types coagulate, which did not seem to contribute to the cognitive effects described in the new study. The researchers speculate that other blood-group differences, such as how likely cells are to stick to one another or to blood vessel walls, might affect brain function.

Cushman emphasizes the need for follow-up studies not only to verify the blood type/brain function association but also to untangle mechanisms for it. In the meantime, those with AB blood need not panic about their future cognitive wherewithal, she says, noting that all our brains are apt to benefit from a healthy diet, awareness of our risk factors for heart disease and stroke, and regular exercise for the body and brain.

- *Andrea Anderson*

From Blood to Brain

Blood type has been linked with a variety of mental disorders, but the associations are weak - many other factors are more important in determining who ends up with an illness. Still, the fact that a connection may exist intrigues some scientists, who hope one day to uncover the biological processes that link blood molecules to mental health, possibly improving our understanding and treatment of these illnesses.

- ***People with O blood type may be more likely to have depression and intense anxiety; children may be at a greater risk of attention-deficit disorder.***
- ***People with A blood type may be more prone to obsessive-compulsive disorder; children may be at a greater risk of attention-deficit disorder.***
- ***Children with B blood type may have a lower risk of attention-deficit disorder.***

- *Victoria Stern*

http://bit.ly/1v7OboR

New one-in-two cancer figure sounds scarier than it is

If you were born in the UK, that is the likelihood you'll be diagnosed with cancer at some point

- **15:28 04 February 2015 by Penny Sarchet**

At least one in two. If you were born in the UK, that is the likelihood you'll be diagnosed with cancer at some point, according to new research funded by Cancer Research UK (CRUK). The estimate replaces the well-known one-in-three statistic for lifetime cancer risk. What lies behind the change?

One-in-three to one-in-two – that's quite an increase. What has caused the big leap in cancer risk?

The new estimate does not reflect some dramatic change in how many of us are dying from cancer since the one-in-three figure was published; rather, it's a correction to that figure. The one-in-three estimate came from a previous CRUK calculation published in 2011, which used a different method to come up with lifetime risk, based on a smaller study group. It looked at UK cancer cases between 2009 and 2011 and used this to calculate the risk. This is now considered an underestimate, as the short time frame doesn't take into account how cancer rates have been changing. The one-in-two figure attempts to capture how lifestyle and disease trends change over decades.

Where does the new figure come from?

It comes from tracking cancer incidence over whole lifetimes for people born in the UK between 1930 and 1960. Pulling together data from the Office of National Statistics and the UK's national cancer registries revealed that a man born in 1930 has a 38.5 per cent risk of developing cancer during his lifetime, whereas a man born in 1960 has a 53.5 per cent risk. In women, the risk was 36.7 per cent for those born in 1930, and 47.5 per cent for those born thirty years later. Assuming that this upward trend in cancer incidence continues, the researchers conclude that

people born since 1960 will have at least a one-in-two chance of getting cancer over their lifetime.

Is it sensible to assume that increasing numbers of us will die from cancer?

It's not too much of a stretch. Some risk factors such as exposure to asbestos have been declining, but others have increased, says Isabelle Soerjomataram from the International Agency for Research on Cancer in Lyon, France. "There are many other cancer risk factors common in industrialised countries which we know have increased over the same period of time, for example, higher body weight and higher exposure to UV. Populations continue to adopt unhealthy lifestyles that are known to increase cancer risks," she says.

Why are people born in 1960 so much more likely to get cancer than people born thirty years earlier?

The ones born in 1960 are likely to live longer. Older people have had more time to acquire genetic mutations, so are more likely to develop the disease. The longer we live, the more cases of cancer we'll see.

People are dying less and less from other diseases and are therefore more likely to be diagnosed with cancer, says Soerjomataram. Another factor is improvement in our ability to detect cancer. Techniques like breast-cancer screening and testing for prostate cancer markers mean cancers are more likely to be identified in the first place, and often at a younger age, which also changes the statistics.

We shouldn't forget that more people are also surviving cancer. Today half of people newly diagnosed with the disease will live for more than 10 years. In the early 1970s, the corresponding survival rate was only 24 per cent.

Can you improve your odds of not getting cancer?

Certainly. More than 40 per cent of cancers diagnosed in the UK in 2010 were associated with lifestyle and environmental factors – meaning you can take some control of your own chances. Unsurprisingly, smoking was the worst offender: nearly 20 per cent of all cancer diagnoses that year were smokers.

The International Agency for Research on Cancer has drawn up a code against cancer, which recommends 11 other ways you can reduce your risk.

Journal reference: British Journal of Cancer, DOI: 10.1038/bjc.2014.606

http://bit.ly/16RlLKC

Life-changing implants reveal intricacy on a chip

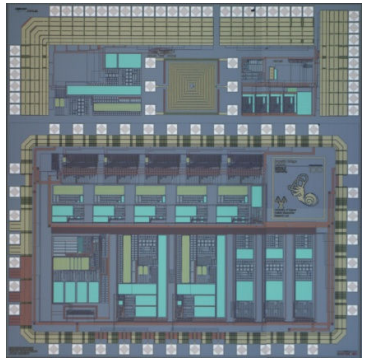
This inner ear implant could one day help people with dizziness and balance disorders to regain stability.

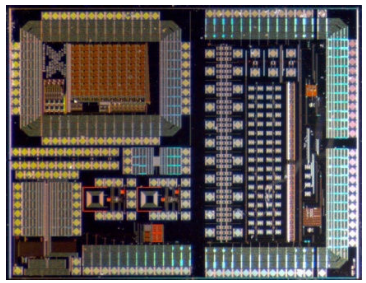
- **18:30 04 February 2015 by Flora Graham**

Developed by Timothy Constandinou from Imperial College London and colleagues, it senses linear and radial acceleration in three dimensions and transforms the information into a signal that the brain can interpret, restoring balance in a similar way to how a cochlear implant fixes hearing.

The chip, which measures 3 × 2 millimetres, is an example of how dramatically implants have shrunk. Early prototypes were bulky and hampered by poor battery life.

To save costs, many different types of implants can be integrated on a single silicon wafer. In the wafer pictured above, the chip in the top right corner, for example, is a prototype designed to connect the severed nerves of people with spinal injuries. The chip in the bottom right is being developed to sense the chemical activity in nerves. The wafer will later be chopped up into separate implants.





Both of these pictures are part of an Instagram series celebrating the beauty of life-changing chips designed by the Centre for Bio-Inspired Technology at Imperial College London.

(Image: Imperial College London)

http://nyti.ms/1DPgtti

Ebola Drug Aids Some in a Study in West Africa

An Ebola treatment center run by the Alliance for International Medical Action has tested the drug favipiravir.

By SHERI FINK FEB. 4, 2015

For the first time, a drug is showing promising signs of effectiveness in Ebola patients participating in a study. The medicine, which interferes with the virus's ability to copy itself, seems to have halved mortality - to 15 percent, from 30 percent - in patients with low to moderate levels of Ebola in their blood, researchers have found. It had no effect in patients with more virus in their blood, who are more likely to die. The drug, approved as an influenza treatment in Japan last year, was generally well tolerated.

"The results are encouraging in a certain phase of the disease," Dr. Sakoba Keita, director of disease control for the Guinean Ministry of Health, said in a telephone interview. The drug is being tested in Guinea, one of the three West African countries most affected by the Ebola crisis.

The details of the early findings have not yet been announced, but they raise questions about which patients, if any, outside the study should be offered treatment with the drug, favipiravir. "These are very difficult, agonizing decisions,"

said Susan Ellenberg, a professor of biostatistics at the University of Pennsylvania's Perelman School of Medicine, who was not involved in the research. She cautioned that early results were sometimes not borne out.

The drug has been provided on an emergency basis to Ebola patients in European countries, but not in Africa. The Japanese maker of the drug announced in October that it had 20,000 courses of treatment in stock. The epidemic is now ebbing but is not over. The World Health Organization on Wednesday reported 124 new cases in Guinea, Sierra Leone and Liberia in the week that ended on Sunday, warning of an increased geographical spread in Guinea and a rise in new cases in all three countries for the first time this year.

Early reports of the interim results of the drug trial have created unanticipated complications, delaying the testing of at least one other therapy as researchers reconsidered plans and some doctors pressed to make favipiravir more widely available.

Avigan, a drug approved as an anti-influenza drug in Japan, is showing promise in treating ebola. **Credit Issei Kato/Reuters**

Researchers and health authorities have been quietly debating whether and when to release the preliminary results of the study. The dilemmas they face echo those from the early years of the AIDS epidemic. Because mortality was so high in a disease with no proven treatment, there was demand to provide experimental therapies to everyone.

The results for the drug favipiravir are based on an analysis of 69 patients older than 14 who have received it at two sites in Guinea since December. The survival rates of those with low to moderate levels of virus in their blood were significantly better than those of patients previously treated at a center run by Doctors Without Borders in Guéckédou, Guinea.

Caroline Guele, 31, a rice farmer who lost two children and her husband to Ebola, received the drug in January at the site run by the Alliance for International Medical Action soon after she developed symptoms. She said she believed it contributed to her survival. "When I heard I could take the medicine, I actually prayed to God it would help me," she said in a telephone interview Wednesday.

Continue reading the main story

In a typical drug study, participants would be randomly assigned to take the drug or not, and the outcomes would be compared to see if the drug made a difference. However, because Ebola is so deadly and there is no known treatment aside from supportive care, all patients in the study were provided with the treatment.

Fluctuating death rates during the current epidemic have complicated researchers' efforts to assess whether the new drug should be credited with the reduced mortality.

The drug was expected to be most effective in patients receiving it within two to three days of showing symptoms, similar to antiviral treatments for influenza. However, most study participants arrived at the Ebola treatment units later in their illnesses, a median of five days after their symptoms began, so results were analyzed instead in terms of the approximate levels of virus in the blood.

Independent boards charged with monitoring the drug trial detected the encouraging findings and recommended that they be made public. Results were submitted for review to the Conference on Retroviruses and Opportunistic Infection, which will take place in Seattle at the end of the month. A draft of an abstract of the findings was reviewed by The New York Times.

"With Ebola, there's precious little good news," said Dr. Susan Shepherd, who served as medical coordinator at a treatment unit run by the Alliance for International Medical Action, one of two sites where the drug was tested. (The other was a facility run by Doctors Without Borders.)

Dr. Shepherd added, "There will, I think, be an enormous pressure and desire to offer the treatment more broadly."

The trial is sponsored by the French public research institute Inserm, with support from the European Union, and is run by a consortium of organizations and the Guinean government. After a briefing with the president of Inserm, President François Hollande of France issued a statement on Wednesday welcoming the findings and calling them an important step. The drug, also known by the trade name Avigan, was developed by the Japanese company Toyama Chemical, part of Fujifilm Group, and approved for influenza treatment in that country last March after safety testing.

The company has said it would produce more doses of the drug in anticipation of the trial. It has also provided the tablets on an emergency basis to several Ebola patients in Europe, according to a company spokeswoman, Kana Matsumoto. She said that the drug had never been provided on that basis to patients in any African country, and that the company had no comment as to whether it would do so in the future given the new findings.

"With a medication that seems to be safe, you really don't have a leg to stand on in terms of this person gets it and this person doesn't," Dr. Shepherd said. "The problem we seem to have is it doesn't help at all for people who have high viral loads."

Researchers hope that some patients' lives might be saved by bolstering the immune system, including through transfusions of serum extracted from the blood of Ebola survivors, which contains virus-fighting antibodies.

However, expectations around favipiravir have contributed to a delay in a trial of serum transfusions, also known as convalescent plasma therapy, in Guinea's capital, according to Roeland Scholtalbers, the head of communications for the Institute of Tropical Medicine in Antwerp, Belgium, the study's sponsor.

If patients getting the serum transfusions also get favipiravir, as some doctors have urged, it would probably be more difficult to discern whether the serum had an effect. Mr. Scholtalbers said that just because early results for favipiravir came first did not mean that researchers or the public should "put more hope on that solution than any other solution." "There are pretty good arguments to think that plasma can give good impact," he continued. "It will be a shame if we don't manage as a scientific community to test it."

Dr. Xavier Anglaret, the lead investigator of the favipiravir trial in Guinea, said that he and his colleagues agreed that the other study was important. "The plasma trial should start as early as possible," he said.

Both trials are all the more important because of the abrupt cancellation last Friday of a study testing a third therapy, the anti-viral drug brincidofovir, after the manufacturer concluded there was an insufficient number of Ebola patients in Liberia, where the trial was underway, to determine the effectiveness of the drug.

Dr. Anglaret said researchers had expected to have results from all three studies around the same time. Instead, one study advanced ahead of the others, with early results that are encouraging but not definitive. As of Tuesday, Dr. Anglaret said, the favipiravir trial had enrolled 101 patients in the continuing study.

The complications of managing the Ebola trials are a sign that more needs to be done to prioritize research in future outbreaks, said Dr. Bernard Lo, a bioethicist and president of the Greenwall Foundation in New York City.

http://www.eurekalert.org/pub_releases/2015-02/f-sf-ndf020515.php

Neanderthals disappeared from the Iberian Peninsula before than from the rest of Europe

New study shows that Neanderthals could have disappeared from the Iberian Peninsula closer to 45,000 years ago

Until a few months ago different scientific articles, including those published in '*Nature*', dated the disappearance of the Neanderthals (*Homo neanderthalensis*) from Europe at around 40,000 years ago. However, a new study shows that these hominids could have disappeared before then in the Iberian Peninsula, closer to 45,000 years ago. A scientific article published in '*Nature*' in August 2014 revealed that the European Neanderthals could have disappeared between 41,000 and 39,000 years ago, according to the fossil remains found at sites located from the Black Sea in Russia to the Atlantic coastline of Spain.

However, in the Iberian Peninsula the Neanderthals may have disappeared 45,000 years ago. This is what has now been revealed by data found at the El Salt site in the Valencian Community (Spain).

"Both conclusions are complementary and not contradictory," confirms Bertila Galván, lead author of the study published in the '*Journal of Human Evolution*' and researcher at the Training and Research Unit of Prehistory, Archaeology and Ancient History at the University of La Laguna (ULL) (Tenerife, Spain).

Until now, there was no direct dating in Spain on the Neanderthal human remains which produced recent dates. "The few that provided dates before 43,000 and 45,000 years ago in all cases," points out Galván, who says that there are more contextual datings. "Those which offer recent dates are usually labelled as dubious or have very small amounts of lithic material that can tell us little," he observes.

The study in '*Nature*' proposes that the point of departure was 40,000 years as "there is almost no evidence of these human groups in the Eurasian region," but it also recognises that the process of disappearance is "complex and manifests itself in a regionalised manner with peculiarities in the different places," adds Galván, who also worked on the '*Nature*' research.

In this context, the new study questions the existence of the Neanderthals in the Iberian Peninsula later than 43,000 years ago. In doing so the team of scientists provided data that referred specifically to the final occupations in El Salt, "a very robust archaeological context" in terms of the reliability of the remains, says the scientist.

The new timeline for the disappearance of the Neanderthals (which also includes "solid and evidence-based" information from other sites in the territory) allows for a regional reading, limited to the Iberian Peninsula; and which coincides with the remains found at other Spanish sites. "These new dates indicate a possible disappearance of the regional Neanderthal populations around 45,000 years ago," indicates the study's research team.

The gradual demise of the Iberian Neanderthals

The ample record of lithic objects and remains of fauna (mainly goats, horses and deer), as well as the extensive stratigraphic sequence of El Salt have allowed the disappearance of the Neanderthals to be dated at a site that covers their last 30,000 years of existence.

Together with this new dating is the discovery of six teeth that probably belonged to a young *Homo neanderthalensis* adult and that "could represent an individual of one of the last groups of Neanderthals which occupied the site and possibly the region," say the scientists.

Analysis with high resolution techniques, which combined palaeoenvironmental and archaeological data, point to "a progressive weakening of the population, or rather, not towards an abrupt end, but a gradual one, which must have been drawn out over several millennia, during which the human groups dwindled in number," as Cristo Hernández, another of the study's authors and researcher at ULL, told SINC.

This gradual disappearance coincided with a change in the climate creating colder and more arid environmental conditions, "which must have had an effect on the lives of these diminishing populations," adds Hernández. The anatomically modern humans had no role in this disappearance, unlike "the significant worsening of the climate, given that their presence in these lands was much later," reveals the researcher.

The new dating establishes depopulation in this region between the last Neanderthals and the first anatomically modern humans. This fact has been archaeologically proven in a sedimentary hiatus that was found not only in El Salt, "but also in other sites on the Iberian Peninsula," conclude the researchers.

B. Galván et al. (2014). "New evidence of early Neanderthal disappearance in the Iberian Peninsula" Journal of Human Evolution 75: 16-27 DOI: 10.1016/j.jhevol.2014.06.002

http://www.eurekalert.org/pub_releases/2015-02/ci-1mm020315.php

15-million-year-old mollusk protein found

A team of Carnegie scientists have found "beautifully preserved" 15 million-year-old thin protein sheets in fossil shells from southern Maryland.

Washington, D.C. - The team - John Nance, John Armstrong, George Cody, Marilyn Fogel, and Robert Hazen - collected samples from Calvert Cliffs, along the shoreline of the Chesapeake Bay, a popular fossil collecting area. They found fossilized shells of a snail-like mollusk called Ecphora that lived in the mid-Miocene era - between 8 and 18 million years ago. Their findings are published in the inaugural issue of Geochemical Perspectives Letters.

Ecphora is known for an unusual reddish-brown shell color, making it one of the most distinctive North American mollusks of its era. This coloration is preserved in fossilized remains, unlike the fossilized shells of many other fossilized mollusks from the Calvert Cliffs region, which have turned chalky white over the millions of years since they housed living creatures.

Shells are made from crystalline compounds of calcium carbonate interleaved with an organic matrix of proteins and sugars proteins and sugars. These proteins are called shell-binding proteins by scientists, because they help hold the components of the shell together. They also contain pigments, such as those responsible for the reddish-brown appearance of the Ecphora shell. These pigments can bind to proteins to form a pigment-protein complex.

The fact that the coloration of fossilized Ecphora shells is so well preserved suggested to the research team that shell proteins bound to these pigments in complex might also be preserved. They were amazed to find that the shells, once dissolved in dilute acid, released intact thin sheets of shell proteins more than a centimeter across. Chemical analysis including spectroscopy and electron microscopy of these sheets revealed that they are indeed shell proteins that were preserved for up to 15 million years.

A 15-million-year-old fossil gastropod, Ecphora, from the Calvert Cliffs of southern Maryland is depicted. The golden brown color arises from the original shell-binding proteins and pigments preserved in the mineralized shell. **John Nance**

"These are some of the oldest and best-preserved examples of a protein ever observed in a fossil shell," Hazen said.

Remarkably, the proteins share characteristics with modern mollusk shell proteins. They both produce thin, flexible sheets of residue that's the same color as the original shell after being dissolved in acid. Of the 11 amino acids found in the resulting residue, aspartate and glutamate are prominent, which is typical of modern shell proteins. Further study of these proteins could be used for genetic analysis to trace the evolution of mollusks through the ages, as well as potentially to learn about the ecology of the Chesapeake Bay during the era in which Ecphora thrived.

This work was supported in part by the NASA Astrobiology Institute, the Deep Carbon Observatory, the Hazen Foundation, and the Carnegie Institution for Science.

http://bit.ly/1vxuwEB

Newly Discovered Networks among Different Diseases Reveal Hidden Connections

Enormous databases of medical records have begun to reveal connections among diseases that could provide insights into the biological missteps that make us sick

February 5, 2015 |By Veronique Greenwood and Quanta Magazine

Stefan Thurner is a physicist, not a biologist. But not long ago, the Austrian national health insurance clearinghouse asked Thurner and his colleagues at the Medical University of Vienna to examine some data for them. The data, it turned out, were the anonymized medical claims records - every diagnosis made, every treatment given - of most of the nation, which numbers some 8 million people. The question was whether the same standard of care could continue if, as had

recently happened in Greece, a third of the funding evaporated. But Thurner thought there were other, deeper questions that the data could answer as well.

In a recent paper in the New Journal of Physics, Thurner and his colleagues Peter Klimek and Anna Chmiel started by looking at the prevalence of 1,055 diseases in the overall population. They ran statistical analyses to uncover the risk of having two diseases together, identifying pairs of diseases for which the percentage of people who had both was higher than would be expected if the diseases were uncorrelated - in other words, a patient who had one disease was more likely than the average person to have the other. They applied statistical corrections to reduce the risk of drawing false connections between very rare and very common diseases, as any errors in diagnosis will get magnified in such an analysis. Finally, the team displayed their results as a network in which the diseases are nodes that connect to one another when they tend to occur together.

The style of analysis has uncovered some unexpected links. In another paper, published on the scientific preprint site arxiv.org, Thurner's team confirmed a controversial connection between diabetes and Parkinson's disease, as well as unique patterns in the timing of when diabetics develop high blood pressure. The paper in the New Journal of Physics generated additional connections that they hope to investigate further.

Eventually, Thurner and a growing number of other researchers hope to use these disease networks to generate hypotheses about how diseases operate at the molecular level. "Is this disease caused by a gene?" Thurner said. "Is it caused by a defect in the metabolic network? Is it due to environmental things that affect certain genes? Things like this. This is the aim."

The work is being driven by the realization that diseases, as defined in medicine, sound like tidy, distinct entities, but are messier in reality. Diseases tend to be defined by their symptoms. But the molecular roots of a disease may have biological effects that go far beyond our current understanding. Certain diseases tend to follow others or have high rates of comorbidity, and though it isn't clear why, it may be because they arise from related biological flaws.

"The idea is, connections at the cellular level get amplified at the population level, and they emerge as comorbidity," said Albert-László Barabási, a physicist at Northeastern University who has published several landmark papers in this area, including a 2009 article in PLOS Computational Biology that helped inspire Thurner, as well as a 2011 review of the field in Nature Reviews Genetics. Using a disease network, a researcher might suggest that biologists look for new disease genes shared between diseases one and two, for instance, where there seems to be a strong connection.

Biologists typically look for genetic connections by using genome-wide association studies, which statistically associate genetic markers with disease. But at Harvard Medical School, another research team is attempting to find the same connections by mapping networks of a very different kind: the molecular networks at work in a cell.

Networks of life

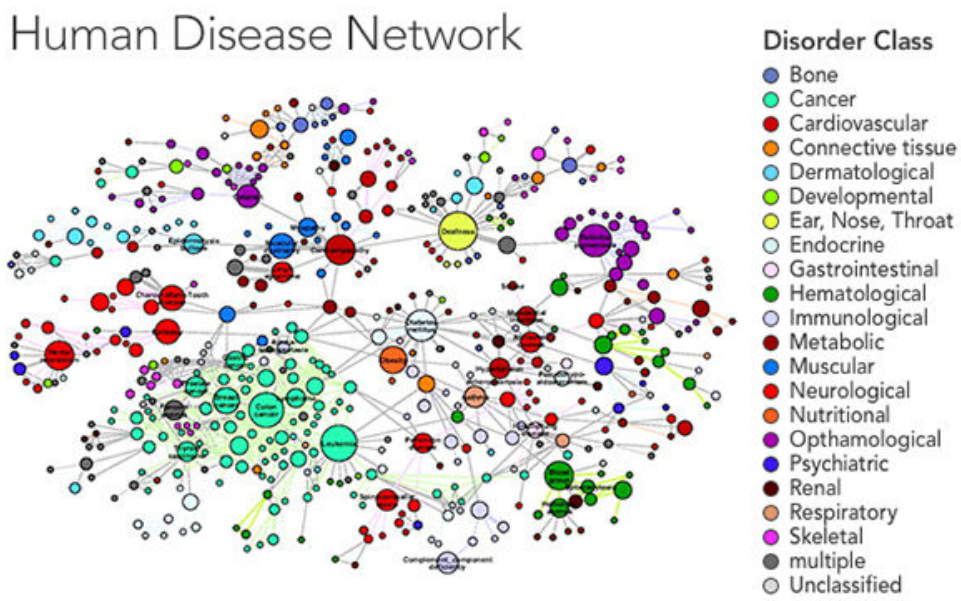
The inside of a cell seethes with activity, as tiny molecules, enormous proteins and strands of DNA wash around each other going about their business. Each actor's business is some set of other actors - a protein, for instance, might snip pieces off of other proteins, ferry molecules around, or jump-start the manufacturing of DNA. It takes its cues from other actors, which can make it work faster or more slowly or send it off to distant regions where it's needed.

The functioning of the cell can take on a very different character if even a single member of this molecular social network starts to behave oddly. Before long, the effects ripple outward from the initial flaw, causing problems - disease - on the level of the organism. A disease is in some sense just an expression of the underlying dynamics of this social structure. Thurner hopes his disease networks can eventually help uncover some of these flaws.

And it's here at the sub-microscopic end of things that Joseph Loscalzo, a professor at Harvard Medical School and a long-time collaborator of Barabási's, is mapping his own network. He and his team start by gleaning data from numerous databases on which proteins interact with each other and how. Then, using a computer model, they sketch out the social network within an average cell, connecting individual genes and proteins to one another if they happen to interact. Loscalzo's team has built a diagram with 13,460 protein nodes and 141,296 links. (These interactions probably account for only about 20 to 25 percent of the total, Loscalzo says, but it's a start.) Then they isolate just the nodes that have been statistically linked to a given disease. They call this set of nodes the disease module.A human disease network maps out connections between diseases - if patients who have one disease tend to also have another, the two disease nodes are connected.

One disease module they've studied is for pulmonary hypertension - high blood pressure in the lungs, which can cause heart failure. They looked at all the molecular pathways that genome-wide association studies suggested were involved. They then studied which pathways grow more active in animal models and in pulmonary hypertension patients under stress. Their disease module revealed that two proteins previously linked to some forms of the disease were part of the same molecular pathway and that they work together to cause errors in

cell proliferation, which may be linked to the symptoms of the disease. The researchers published their findings in the journal Pulmonary Circulation.



Credit: Olena Shmahalo/Quanta Magazine; source: Albert-László Barabási

Another module looks at Type 2 diabetes. Researchers have linked diabetes to about 200 spots on the genome through genome-wide association studies. "The first 18 or so of those are highly significant, but the last 182 or so are just at the margin," Loscalzo said. But in the disease module, it was clear that some of those 182 genes were highly connected hubs in the social network, a state of affairs that a genome-wide association study alone is not equipped to reveal. "We've explored three of those [genes] now, and they highlight pathways that had been peripherally believed to be associated with diabetes but never demonstrated in any careful way," he said.

Combining Loscalzo's molecular networks with Thurner and Barabási's disease networks would help to create a bridge between correlation and mechanism. If comorbid diseases share overlapping molecular networks, researchers could use the networks to understand the biochemical mechanisms behind them. These two kinds of networks, very different in how they are built, are united only by the idea that data can reveal connections that otherwise would pass unnoticed. But together these networks have the potential to open new doors in the study of disease.

"Once you draw a network, you are drawing hypotheses on a piece of paper," Thurner said. "You are saying, 'Wow, look, I didn't know these two things were related. Why could they be? Or is it just that our statistical threshold did not kick it out?'" In network analysis, you first validate your analysis by checking that it recreates connections that people have already identified in whatever system you are studying. After that, Thurner said, "the ones that did not exist before, those are new hypotheses. Then the work really starts."

It is worth remembering that both techniques are still relatively new. Loscalzo can reel off ways that his results could be flawed - the sprawling incompleteness of the data on protein-protein interactions is a major concern, but so are the methods used to gather the data, which are the best currently possible but far from perfect. And Thurner and his students are still gathering collaborators in biology who can test their hypotheses. After they published their first results from the database a couple of years ago, Thurner said wryly, "we thought we would have a hundred people sitting in our office," looking to collaborate. So far, the response has been more of a trickle.

"It's not uncontroversial," said Andrey Rzhetsky, a professor of genetics at the University of Chicago with a background in mathematical biology who has published on comorbidity networks. "Some people feel very strongly about big data sets - almost to the point of fanatic refusal to accept results from large-scale analysis." The argument, he explains, is that there are unknown biases in large data sets. In the case of databases like Thurner's, these biases stem from the different ways doctors enter information into medical records, the way ethnicity is accounted for, and so on. Rzhetsky acknowledges the danger of biases but believes they do not eliminate the usefulness of the data, provided researchers are careful with their interpretations. "I do think it's the direction for the future, but it's far from a solved problem," he said. He was intrigued by the article in the New Journal of Physics. "The model is extremely simple, but the direction is great," he wrote in an email.

Loscalzo is aware of his colleagues' scrutiny. "When I give talks about network medicine," he said, "I've gotten three kinds of responses. At one end of the spectrum are generally young people … who say this is a great idea, I hadn't thought about this before. … At the other end of the spectrum I have people my age or older who say: 'What are you talking about? I'm a member of the National Academy and that's all based on reductionist biology, I'm not going to change my strategy.' Then in the middle you've got this broad swath of people who have a healthy skepticism and who want there to be some sort of proof that these notions can give us new insights. And that's what we've been working on."

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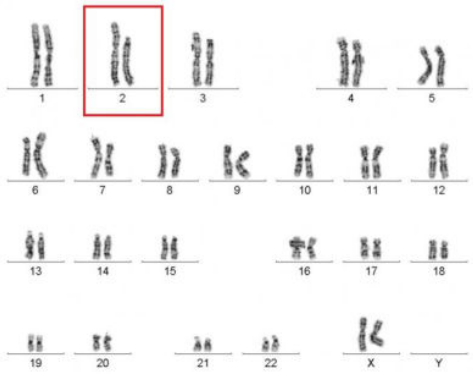
http://www.eurekalert.org/pub_releases/2015-02/nioa-nrd020215.php

NIH researchers describe spontaneous cure of rare immune disease

Chromothripsis may have spontaneously cured the first person to be documented with WHIM syndrome

A genetic phenomenon called chromothripsis, or "chromosome shattering," may have spontaneously cured the first person to be documented with WHIM syndrome, according to researchers at the National Institutes of Health (NIH). The patient was the subject of a 1964 study that first described the disorder, a syndrome of recurrent infections, warts and cancer caused by the inability of immune cells, particularly

bloodstream. In 2003, researchers identified the genetic mutations responsible for the disease, which occur in the CXCR4 gene.



As an adult, the patient contacted NIH's National Institute of Allergy and Infectious Diseases (NIAID) to evaluate herself and two of her children, who eventually were diagnosed with WHIM syndrome. The patient reported that her symptoms resolved in her 30s, indicating that she had maintained disease remission for nearly 20 years.

This is an image of all 46 chromosomes of the cured WHIM syndrome patient shows that one copy of chromosome 2 (red box) is significantly shorter than the other, a loss of genetic material caused by chromothripsis. As a result of this random event, the patient experienced a fortuitous deletion of a mutant copy of the gene responsible for WHIM syndrome - CXCR4 - in the immune cells most affected by the mutation.

infection-fighting neutrophils, to leave the bone marrow and enter the In their study, NIAID researchers identify chromothripsis, the abrupt fragmentation of a chromosome, as the reason for the cure. Such severe changes often cause cells to die, unless they confer a survival advantage, which occurs during the development of some cancers. The researchers show that chromothripsis caused a random and fortuitous deletion of the mutant CXCR4 gene in the patient. Presumably, a stem cell lacking mutant CXCR4 survived and eventually repopulated all of the patient's neutrophils, which now appear to function normally. The study is the first to link chromothripsis to a positive outcome.

There currently are no approved treatments for WHIM syndrome, but NIAID scientists are evaluating the drug plerixafor in clinical trials with promising results. Researchers also are exploring how to apply the study findings to improve bone marrow transplantation, which relies on the ability of donor stem cells to *repopulate in a recipient.*

McDermott DH et al. Chromothriptic cure of WHIM syndrome. Cell DOI:10.1016/j.cell.2015.01.014 (2015).

Philip Murphy, M.D., Section Chief, David McDermott, M.D., Staff Clinician and Ji-Liang Gao, Ph.D., Staff Scientist in the Molecular Signaling Section of NIAID's Laboratory of Molecular Immunology are available to discuss the findings.

http://www.eurekalert.org/pub_releases/2015-02/cp-amc012915.php

After merger, chimpanzees learned new grunt for 'apple'

Chimpanzees have special grunts for particular types of foods, and their fellow chimps know exactly what those calls mean.

Now, by studying what happened after two separate groups of adult chimpanzees moved in together at the Edinburgh Zoo, researchers have made the surprising discovery that our primate cousins can change those referential grunts over time, to make them sound more like those of new peers.

The findings, reported in the Cell Press journal Current Biology on February 5, suggest that human language isn't as unique as we thought in its ability to reference external objects with socially learned symbols.

Audio *In 2010, Frek (a Dutch chimp) has high pitched grunts (sound file 1) compared to Lucy (an Edinburgh chimp).* Watson et al.

"Our study shows that chimpanzee referential food calls are not fixed in their structure and that, when exposed to a new social group, chimpanzees can change their calls to sound more like their group mates," says Katie Slocombe of the University of York.

Scientists had generally accepted that the acoustic structure of chimpanzee calls was fixed, with the differences primarily a matter of the animals' arousal state. That apparent lack of flexible control over their referential vocalizations had even been considered a key discontinuity with human language.

However, Slocombe and her colleagues found that the acoustic structure of referential food grunts produced by two groups of adult chimpanzees converged over the course of three years, as its members got to know each other better. That acoustic convergence had nothing to do with individual food preferences, either. The researchers used audio analysis to demonstrate the convergence of structure, but they could also hear the difference.

"We think it's quite easy to hear how the two groups called in different ways for apples in 2010, and how by 2013 the Dutch individuals changed their grunts to sound more like Edinburgh individuals," says Stuart Watson, also from the University of York.

The researchers say that the findings "represent the first evidence of non-human animals actively modifying and socially learning the structure of a meaningful referential vocalization" from other members of their species. Given the relatively short evolutionary distance between humans and chimpanzees - five to seven million years - it also suggests that our most recent common ancestor with chimpanzees also shared this "building block" of language.

"It would be really exciting to try and find out why chimpanzees are motivated to sound more similar to their group mates," adds Simon Townsend of the University of Zurich, who was also involved in the study. "Is it so that they can be better understood? Or is it just to sound more similar to their friends?"

Current Biology, Watson et al.: "Vocal Learning in the Functionally Referential Food Grunts of Chimpanzees"

http://www.eurekalert.org/pub_releases/2015-02/teia-svp020415.php

Seafloor volcano pulses may alter climate

New data show strikingly regular patterns, from weeks to eons

Vast ranges of volcanoes hidden under the oceans are presumed by scientists to be the gentle giants of the planet, oozing lava at slow, steady rates along mid-ocean ridges. But a new study shows that they flare up on strikingly regular cycles, ranging from two weeks to 100,000 years - and, that they erupt almost exclusively during the first six months of each year.

The pulses - apparently tied to short- and long-term changes in earth's orbit, and to sea levels - may help trigger natural climate swings. Scientists have already speculated that volcanic cycles on land emitting large amounts of carbon dioxide might influence climate; but up to now there was no evidence from submarine volcanoes. The findings suggest that models of earth's natural climate dynamics, and by extension human-influenced climate change, may have to be adjusted. The study appears this week in the journal Geophysical Research Letters.

"People have ignored seafloor volcanoes on the idea that their influence is small - but that's because they are assumed to be in a steady state, which they're not," said the study's author, marine geophysicist Maya Tolstoy of Columbia University's Lamont-Doherty Earth Observatory.

"They respond to both very large forces, and to very small ones, and that tells us that we need to look at them much more closely." A related study by a separate team this week in the journal Science bolsters Tolstoy's case by showing similar long-term patterns of submarine volcanism in an Antarctic region Tolstoy did not study.

Volcanically active mid-ocean ridges crisscross earth's seafloors like stitching on a baseball, stretching some 37,000 miles. They are the growing edges of giant tectonic plates; as lavas push out, they form new areas of seafloor, which comprise some 80 percent of the planet's crust.

Conventional wisdom holds that they erupt at a fairly constant rate - but Tolstoy finds that the ridges are actually now in a languid phase. Even at that, they produce maybe eight times more lava annually than land volcanoes. Due to the chemistry of their magmas, the carbon dioxide they are thought to emit is currently about the same as, or perhaps a little less than, from land volcanoes - about 88 million metric tons a year. But were the undersea chains to stir even a little bit more, their CO2 output would shoot up, says Tolstoy.

Some scientists think volcanoes may act in concert with Milankovitch cycles - repeating changes in the shape of earth's solar orbit, and the tilt and direction of its axis - to produce suddenly seesawing hot and cold periods. The major one is a 100,000-year cycle in which the planet's orbit around the sun changes from more or less an annual circle into an ellipse that annually brings it closer or farther from the sun. Recent ice ages seem to build up through most of the cycle; but then things suddenly warm back up near the orbit's peak eccentricity. The causes are not clear.

Enter volcanoes. Researchers have suggested that as icecaps build on land, pressure on underlying volcanoes also builds, and eruptions are suppressed. But when warming somehow starts and the ice begins melting, pressure lets up, and eruptions surge. They belch CO2 that produces more warming, which melts more ice, which creates a self-feeding effect that tips the planet suddenly into a warm period.

A 2009 paper from Harvard University says that land volcanoes worldwide indeed surged six to eight times over background levels during the most recent deglaciation, 12,000 to 7,000 years ago. The corollary would be that undersea volcanoes do the opposite: as earth cools, sea levels may drop 100 meters, because so much water gets locked into ice. This relieves pressure on submarine volcanoes, and they erupt more. At some point, could the increased CO2 from undersea eruptions start the warming that melts the ice covering volcanoes on land?

That has been a mystery, partly because undersea eruptions are almost impossible to observe. However, Tolstoy and other researchers recently have been able to closely monitor 10 submarine eruption sites using sensitive new seismic instruments. They have also produced new high-resolution maps showing outlines

of past lava flows. Tolstoy analyzed some 25 years of seismic data from ridges in the Pacific, Atlantic and Arctic oceans, plus maps showing past activity in the south Pacific.

The long-term eruption data, spread over more than 700,000 years, showed that during the coldest times, when sea levels are low, undersea volcanism surges, producing visible bands of hills. When things warm up and sea levels rise to levels similar to the present, lava erupts more slowly, creating bands of lower topography.

Tolstoy attributes this not only to the varying sea level, but to closely related changes in earth's orbit. When the orbit is more elliptical, Earth gets squeezed and unsqueezed by the sun's gravitational pull at a rapidly varying rate as it spins daily - a process that she thinks tends to massage undersea magma upward, and help open the tectonic cracks that let it out. When the orbit is fairly (though not completely) circular, as it is now, the squeezing/unsqueezing effect is minimized, and there are fewer eruptions.

The idea that remote gravitational forces influence volcanism is mirrored by the short-term data, says Tolstoy. She says the seismic data suggest that today, undersea volcanoes pulse to life mainly during periods that come every two weeks. That is the schedule upon which combined gravity from the moon and sun cause ocean tides to reach their lowest points, thus subtly relieving pressure on volcanoes below. Seismic signals interpreted as eruptions followed fortnightly low tides at eight out of nine study sites.

Furthermore, Tolstoy found that all known modern eruptions occur from January through June. January is the month when Earth is closest to the sun, July when it is farthest - a period similar to the squeezing/unsqueezing effect Tolstoy sees in longer-term cycles. "If you look at the present-day eruptions, volcanoes respond even to much smaller forces than the ones that might drive climate," she said.

Daniel Fornari, a senior scientist at Woods Hole Oceanographic Institution not involved in the research, called the study "a very important contribution." He said it was unclear whether the contemporary seismic measurements signal actual lava flows or just seafloor rumbles and cracking. But, he said, the study "clearly could have important implications for better quantifying and characterizing our assessment of climate variations over decadal to tens to hundreds of thousands of years cycles."

Edward Baker, a senior ocean scientist at the National Oceanic and Atmospheric Administration, said, "The most interesting takeaway from this paper is that it provides further evidence that the solid Earth, and the air and water all operate as a single system."

The research for this paper was funded in large part by the U.S. National Science Foundation.

http://www.bbc.com/news/health-31145604

Flu vaccine 'barely effective' against main viral strain

This year's seasonal flu vaccine is barely able to protect people from the main strain of flu being spread in the UK, health officials say.

By James Gallagher

Doctors are being urged to use antiviral drugs quickly to protect vulnerable patients.

Evidence shows the vaccine is stopping only three out of every 100 vaccinated people from developing symptoms. But Public Health England says people should still get vaccinated to protect against other strains of flu.

Flu is a constantly shifting target and that makes it difficult to develop a vaccine. It is why a new jab is needed each year.

Twelve months ago, the World Health Organization settled on the three most likely strains of flu that would be circulating this winter.

But one of them has since mutated so significantly that the vaccine seems to offer little protection.

It works in just three out of every 100 people. A flu vaccine normally works in 50 out of every 100.

Deadly

The strain in question, H3N2, is also a particular worry as it primarily kills the elderly. There have been outbreaks in care homes and overall there has been a higher-than-expected number of deaths in elderly people this year.

Prof Nick Phin, from Public Health England, told the BBC: "We have seen an increase in excess deaths, probably the biggest increase we've seen since 2008-09, so I'm sure that a significant contribution to this will have been the vaccine not being as effective as it usually is."

Public Health England reached the conclusion after a study on 1,314 patients hospitalised with flu in the UK.

Similar levels of viral mutation have been reported in the US and Canada.

The mutation was also detected in the Australian flu season - during the northern hemisphere's summer - but the vaccine was already in development.

Public Health England has already said this is the worst flu season out of the past three years, but is circulating at nowhere near epidemic levels.

'Get vaccinated'

Dr Richard Pebody, the head of flu surveillance at Public Health England, said: "Throughout the last decade, there has generally been a good match between the strains of flu in the vaccine and those that subsequently circulate, so it's crucial that these results do not discourage people in at-risk groups from having flu vaccination now, or in the future."

He said the vaccine would still protect against swine flu and influenza B, "both of which may yet circulate this season" so he urged at-risk people to get vaccinated.
He added: "Our findings also mean that the early use of antivirals to treat and help prevent serious cases of flu in vulnerable patients is even more important this season."
The deputy chief medical officer, John Watson, said: "The latest data show that levels of flu are generally decreasing in the UK.
"We do see 'drift' in the flu virus from time to time, but even so, I want to reassure people that it is still the best overall way to protect yourself and your family from flu, along with good hand hygiene. "Antiviral drugs are available and effective, and doctors should prescribe them for those at greatest risk of becoming seriously ill due to flu."

http://bit.ly/1DsxNWX

Radar Makes All Houses Glass

Law enforcement agencies have handheld radar that can "see" through walls via RF signals, raising Fourth Amendment concerns.
Larry Greenemeier reports

Download MP3

Doppler radar has been a weather forecaster's best friend for decades. But more recently law enforcement has found another application. For the past two years the FBI, U.S. Marshals and other agencies have used a handheld Doppler radar machine to conduct surveillance through solid walls. That's according to *USA Today*.
Called the Range-R, this Doppler device sends radio frequency signals through concrete, wood and other nonmetal building materials and can measure the distance between itself and any moving objects on the other side. The Range-R can detect even subtle motion like breathing, although it can't yet identify whether the respiration is coming from a person or their pet. Some 200 of the $6,000 devices have been sold.
The problem is that law enforcement has used the Range-R sort of "under the radar," if you will, sometimes employing it without a search warrant. The issue was brought to light in a court case after the device helped U.S. Marshals catch a parole violator at a house in Wichita. Federal appeals court judges were not pleased.
So that's the current situation: police use of the technology to gain an edge versus concerns about violations of Fourth Amendment protections against unreasonable searches. Stay tuned for the developing legal decisions regarding this particular Doppler effect.

http://www.eurekalert.org/pub_releases/2015-02/osu-art020515.php

Another reason to drink wine: It could help you burn fat

Consuming dark-colored grapes might help people better manage obesity and related metabolic disorders

CORVALLIS, Ore. - Drinking red grape juice or wine - in moderation - could improve the health of overweight people by helping them burn fat better, according to a new study coauthored by an Oregon State University researcher.
The findings suggest that consuming dark-colored grapes, whether eating them or drinking juice or wine, might help people better manage obesity and related metabolic disorders such as fatty liver.
Neil Shay, a biochemist and molecular biologist in OSU's College of Agricultural Sciences, was part of a study team that exposed human liver and fat cells grown in the lab to extracts of four natural chemicals found in Muscadine grapes, a dark-red variety native to the southeastern United States.
One of the chemicals, ellagic acid, proved particularly potent: It dramatically slowed the growth of existing fat cells and formation of new ones, and it boosted metabolism of fatty acids in liver cells.
These plant chemicals are not a weight-loss miracle, cautions Shay. "We didn't find, and we didn't expect to, that these compounds would improve body weight," he said. But by boosting the burning of fat, especially in the liver, they may improve liver function in overweight people.
"If we could develop a dietary strategy for reducing the harmful accumulation of fat in the liver, using common foods like grapes," Shay said, "that would be good news."
The study, which Shay conducted with colleagues at the University of Florida and University of Nebraska, complements work with mice he leads at his OSU laboratory. In one 2013 trial, he and his graduate students supplemented the diets of overweight mice with extracts from Pinot noir grapes harvested from Corvallis-area vineyards.
Some of the mice were fed a normal diet of "mouse chow," as Shay calls it, containing 10 percent fat. The rest were fed a diet of 60 percent fat - the sort of unhealthy diet that would pile excess pounds on a human frame.
"Our mice like that high-fat diet," said Shay, "and they overconsume it. So they're a good model for the sedentary person who eats too much snack food and doesn't get enough exercise."
The grape extracts, scaled down to a mouse's nutritional needs, were about the equivalent of one and a half cups of grapes a day for a person. "The portions are reasonable," said Shay, "which makes our results more applicable to the human diet."

Over a 10-week trial, the high-fat-fed mice developed fatty liver and diabetic symptoms - "the same metabolic consequences we see in many overweight, sedentary people," Shay said.

But the chubby mice that got the extracts accumulated less fat in their livers, and they had lower blood sugar, than those that consumed the high-fat diet alone.

Ellagic acid proved to be a powerhouse in this experiment, too, lowering the high-fat-fed mice's blood sugar to nearly the levels of the lean, normally fed mice.

When Shay and his colleagues analyzed the tissues of the fat mice that ate the supplements, they noted higher activity levels of PPAR-alpha and PPAR-gamma, two proteins that work within cells to metabolize fat and sugar.

Shay hypothesizes that the ellagic acid and other chemicals bind to these PPAR-alpha and PPAR-gamma nuclear hormone receptors, causing them to switch on the genes that trigger the metabolism of dietary fat and glucose. Commonly prescribed drugs for lowering blood sugar and triglycerides act in this way, Shay said.

The goal of his work, he added, is not to replace needed medications but to guide people in choosing common, widely available foods that have particular health benefits, including boosting metabolic function.

"We are trying to validate the specific contributions of certain foods for health benefits," he said. "If you're out food shopping, and if you know a certain kind of fruit is good for a health condition you have, wouldn't you want to buy that fruit?"

The research was supported by the Institute of Food and Agricultural Science at the University of Florida and Florida Department of Agriculture and Consumer Services. The study appears in the January issue of the Journal of Nutritional Biochemistry.

Shay's research with mice was supported by the Blue Mountain Horticultural Society, the Erath Family Foundation, and the OSU College of Agricultural Sciences.

http://bit.ly/1urCOgk

Does drinking alcohol - even heavily - protect against ALS?

Everyone knows that ALS is a very bad disease, an awareness underscored by the recent Ice Bucket Challenge.

By Gary Stix

The death of neurons that results in paralysis can be caused by specific genetic mutations. But in most cases, single genes are not the culprit. So researchers have looked for other risk factors that might play a role.

Studies have tagged cigarette smoking as a definite danger. Alcohol, another plausible suspect, has yielded equivocal results in previous investigations. To get a better read on ethanol (some earlier studies were small), researchers from Sweden's Lund University looked at giant medical registries from that country, compiled at various times between 1973 and 2010.

They found that individuals who were classified as problem drinkers were a little more than half as likely to be diagnosed with ALS as those who didn't have "alcohol use disorder." More than 420,000 problem drinkers were registered during the period surveyed - and there were 7965 patients who received an ALS diagnosis.

The study, just reported in *The European Journal of Neurology*, controlled for gender, education and place of birth, among other factors. But it was unable to tell why drinking might help. It did lead, though, to a number of intriguing speculations. The researchers cited studies in rats, done by other groups, that indicated that ingestion of alcohol decreased the number of brain cells called astrocytes that bore high levels of a certain protein linked to the pathology of ALS.

Another obvious question is how Bud Lights or a Johnny Walker Black on the rocks might be prescribed as preventive therapies. The researchers wondered whether an individual with a gene that causes ALS might help fend off the disease by imbibing.

As always, the more-research-is-needed mantra resonates. Further investigations would be worthwhile, though. There is only one approved drug for ALS, and it only buys patients an additional three to six months. If wine, beer or spirits could help with prevention - even in the small number of patients with familial mutations - it might be worth a shot, or three.

Update: A site called ALS Advocacy responded to this post with a great tweet, included here:

"People who have struggled with alcoholism may not have ALS diagnosed promptly or at all. Slurred speech. Stumbling. Will doc look for ALS?"

http://www.medscape.com/viewarticle/839364

Dogs Give Love, Improve Outcomes in Cancer Study

Emotional and social well-being scores increased when cancer patients interacted with dogs during concurrent chemotherapy and radiation therapy sessions, a single-group study has shown.

Nick Mulcahy

Predictably, functional and physical well-being scores plummeted during this "horrible" time for patients, said lead investigator Stewart Fleishman, MD, from the Continuum Cancer Centers of New York at Beth Israel Medical Center in New York City.

"Usually, all four of these [well-being] scores track together and everything goes down," Dr Fleishman told *Medscape Medical News* in an interview.

Anecdotally, patients said they were boosted by the "unconditional love" from the pets and the "friendly dedication" of the pet handlers who brought the animals to the clinic, the investigators report.

One patient told Dr Fleishman, "I would have stopped treatment a few weeks ago, but I wanted to see the dog." The study was published in January issue of the *Journal of Community and Supportive Oncology*.

The multimodality treatment was "intense" and rough on the patients, who all had head and neck cancers, and caused adverse effects such as pain, fatigue, skin lesions, and the inability to swallow solid food or speak, he said.

During the pet visits, "the patient and dog interacted in the usual ways," the investigators explain, "by petting, talking, and playing." The visits took place in the radiation therapy waiting area, chemotherapy suite, or hospital rooms.

All 37 patients were treated at Beth Israel. The head and neck malignancies included oropharyngeal cancer (62%), hypopharynx cancer (11%), and esophageal cancer (8%). Most patients (81%) had stage IV disease.

The average number of clinic visits was 18 (for either chemotherapy or radiation). The average patient was 57 years of age, and 68% of the study cohort was male.

Over the 7-week study period, patients underwent "marked and significant" declines in physical well-being ($P < .001$) and functional well-being ($P = .003$), as measured by the standard Functional Assessment of Cancer Therapy–General scale, the investigators report.

However, social well-being increased significantly ($P = .03$), as did emotional well-being ($P = .004$), after declines in physical well-being at the assessment timepoints (baseline, 3 weeks, and 7 weeks) were controlled for.

"We were amazed at the effect size," Dr Fleishman said.

We were amazed at the effect size.

Bonding with animals has "long been recognized" by healthcare providers as being beneficial to human life, but "little research has been able to substantiate those claims with data," said Judy Gilmer, PhD, RN, from the Vanderbilt University School of Nursing in Nashville, Tennessee, who was not involved in the study.

"This study begins to address an important gap in the literature," she told *Medscape Medical News* in an email.

This study begins to address an important gap in the literature.

On the first day of treatment, study participants met their certified therapy dog, which had been trained by The Good Dog Foundation, a New York–based animal-assisted therapy organization.

Before each "animal-assisted visit" (AAV), the dog is bathed and groomed. In addition, for health and safety reasons, the handler wipes a dog's paws before entering the waiting or treatment room.

"The dog's paws are the most significant issue," Dr Fleishman explained. "We use antibacterial wipes that are not too drying on their paws."

The patients are not the only beneficiaries. "Even the staff enjoys it. Instead of seeing glum patients, they see good cheer in the midst of a horrible time," he reported.

It is difficult to do a randomized clinical trial with the dogs, Dr Fleishman noted. For one thing, there is the problem of "crossover" in a single-clinic design, because the dogs typically interact with multiple patients in waiting rooms. However, a randomized trial is currently looking at the effect of dog visits on children with cancer.

The Canines and Childhood Cancer study is examining the impact of animal-assisted therapy on children newly diagnosed with cancer, their families, and even the therapy dogs who visit them, as reported by *Medscape Medical News*. The trial involves about 30 dogs and more than 100 children from five pediatric hospitals in the United States. Dr Gilmer is one of that trial's investigators.

There has been a long history of using animals to improve human health.

The first documented study suggesting a beneficial effect of animals on human well-being was conducted in the 18th century at the York Retreat, a psychiatric facility started by Quakers in the United Kingdom, "where residents wandered freely around courtyards stocked with animals and birds," Dr Fleishman and colleagues write.

They conclude that their study "justifies the formation of community cancer center partnerships to make the use of AAVs a viable option."

"Most cancer centers" now have animal visits, Dr Fleishman said. He explained that in his work as a surveyor for accreditation for the American College of Surgeons Commission on Cancer, he has visited about 50 cancer centers, and the majority have AAVs.

This study was supported by grants from The Good Dog Foundation and Zoetis Animal Health. Dr Fleishman and Dr Gilmer have disclosed no relevant financial relationships.

J Community Support Oncol. 2015;13:22-26. Abstract

http://s.nikkei.com/16zJsG8

Japan's Akatsuki probe to attempt Venus orbit again

A Japanese space probe launched five years ago will on Dec. 7 try for the second and possibly final time to get into orbit around Venus, the Japan Aerospace Exploration Agency announced Friday.

TOKYO - Akatsuki, meaning "dawn" in Japanese, was designed to orbit Venus and take atmospheric readings. It was launched in May 2010 using an H-IIA rocket. JAXA attempted to insert the probe into Venus orbit on Dec. 7 of that year, but a problem with a fuel supply valve caused the main engine to stop. Akatsuki is now in a heliocentric orbit slightly inside that of the planet.

The probe's four attitude control rockets will be used in place of the main engine to decelerate it and bring it into orbit around Venus. Its trajectory will be corrected in July in preparation for the attempt in December.

Akatsuki's thrust is down to just 20% of that originally planned for orbit insertion. JAXA had intended to put the probe into an elliptical orbit with a 30-hour period and a maximum distance of about 80,000km, but this has been adjusted to an eight- to nine-day period and a maximum distance of around 320,000km.

If the probe fails this time as well, low fuel would make a third try difficult.

Feb. 11 and August will be critical points for the mission. Akatsuki will pass closer to the sun, exposing it to higher temperatures than anticipated when it was designed.

Venus is about the same size as Earth and believed to be very similar. But the two planets have dramatically different climates, with 100-meter-per-second winds blowing through the Venusian upper atmosphere. If successfully brought into orbit, Akatsuki will examine atmospheric movement in three dimensions to hopefully shed light on the mechanism behind this circulation.

None of Japan's planetary orbiter projects have met with success so far. In 2003, the Nozomi probe failed to achieve Mars orbit. Meanwhile, countries including the U.S. have put spacecraft into orbit around Mars and Pluto. In 2014, India ***became the first Asian country with a successful Mars orbiter.***

http://www.eurekalert.org/pub_releases/2015-02/bs-wni020415.php

What's next in diets: Chili peppers?

Researchers at the University of Wyoming discover that adding capsaicin from chili peppers to a diet can help to prevent weight gain in mice on high-fat diet

WASHINGTON - Don't go chomping on a handful of chili peppers just yet, but there may be help for hopeful dieters in those fiery little Native American fruits.

A large percentage of the world's population - fully one third, by the World Health Organization's estimates - is currently overweight or obese. This staggering statistics has made finding ways to address obesity a top priority for many scientists around the globe, and now a group of researchers at the University of Wyoming has found promise in the potential of capsaicin - the chief ingredient in chili peppers - as a diet-based supplement.

The temptation to eat fatty foods is often so strong that, for many, it can override or overpower any dietary restrictions. As a solution to this problem, a group of researchers at the University of Wyoming developed a novel approach to stimulate energy metabolism - without the need to restrict calorie intake.

During the Biophysical Society's 59th Annual Meeting in Baltimore, Md., Feb. 7-11, 2015, the researchers from the laboratory of Dr. Baskaran Thyagarajan, University of Wyoming will describe how dietary capsaicin may stimulate thermogenesis and energy burning by activating its receptors, which are expressed in white and brown fat cells. This may help to prevent and manage obesity and other related health complications such as Type 2 diabetes, high blood pressure, and cardiovascular diseases - though this effect has not yet been demonstrated in carefully-controlled clinical trials.

"Obesity is caused by an imbalance between calorie intake and energy dissipation," explained Vivek Krishnan, a graduate student working in Baskaran Thyagarajan's laboratory at the University of Wyoming's School of Pharmacy - a research group known as "Baskilab."

"In our bodies, white fat cells store energy and brown fat cells serve as thermogenic (heat produced by burning fat) machinery to burn stored fat. Eating calorie-rich food and a lack of physical activity cause an imbalance in metabolism that leads to obesity."

While pursuing a strategy for obesity management, our group's laboratory data revealed that "dietary capsaicin - a chief 'agonist' (initiator of a response) of transient receptor potential vanilloid 1 (TRPV1) channel protein - suppresses high-fat-diet-induced obesity," Krishnan said.

Baskilab has found that high-fat-diet obesity and dietary capsaicin - 0.01 percent of capsaicin in the total high fat diet - prevented high-fat-diet-induced weight gain in trials with wild type mice, but not in mice that genetically lacked TRPV1.

Further, dietary capsaicin didn't modify food or water intake in these mice, "although it did significantly increase the metabolic activity and energy expenditure in wild type mice fed a high-fat diet, "but not for mice that genetically lack TRPV1" Krishnan noted.

So, Baskilab's overarching hypothesis is that dietary capsaicin induces browning of white adipose tissue and stimulates thermogenesis to counteract obesity. "The main goal of our work is to expand the knowledge of the mechanism by which capsaicin antagonizes obesity, as well as to advance the proof of principle of the anti-obesity potential of dietary capsaicin. Next, we'll focus on our longer-term goal of developing TRPV1 agonists as new drug molecules to prevent and treat obesity," said researchers from Baskilab.

Developing a natural dietary supplement as a strategy to combat obesity can be easily advanced to human clinical trials, according to the researchers. "We envision a nanoparticle-based sustained-release formulation of capsaicin, which is currently under development in our laboratory," added researchers from Baskilab. "In turn, this will advance a novel dietary supplement-based approach to prevent and treat one of the life-threatening diseases, obesity and its associated complications - in humans."

The group's strategy to counteract obesity is expected to form a major focus of future healthcare priorities for both the National Institutes of Health and Department of Defense.

Baskilab has already submitted a patent application for the drug delivery aspect of the discovery.

The poster #B399, "Dietary capsaicin and exercise: analysis of a two-pronged approach to counteract obesity" by Vivek Krishnan, Kevin Fettel and Baskaran Thyagarajan, will be in a poster session beginning at 1:45 p.m. on Sunday, February 8, 2015 in Hall C of the Baltimore Convention Center. ABSTRACT: http://tinyurl.com/kjq6tpp

http://www.eurekalert.org/pub_releases/2015-02/uotm-sie020615.php

Study identifies 8 signs associated with impending death in cancer patients

MD Anderson research may aid physicians' ability to prognosticate, help patients and families make difficult personal, treatment decisions

Researchers at The University of Texas MD Anderson Cancer Center have identified eight highly specific physical and cognitive signs associated with imminent death in cancer patients. The findings, published in the journal Cancer, could offer clinicians the ability to better communicate with patients and families. They may also guide both the medical team and caregivers on complex decision making, such as discontinuation of tests and therapy, plans for hospital discharge and hospice referral.

Previous studies in end-of-life care have focused on physicians prognosticating better. However, according to David Hui, M.D., assistant professor, Palliative Care and Rehabilitation Medicine, research on how to tell if a patient has entered the final days of life has been minimal. Knowing with a high degree of confidence that death is imminent could have significant implications for clinical practice. It may also help families and caregivers make more informed decisions.

"In the past, studies trying to understand the signs associated with impending death were conducted in people who were recognized as dying, so there's a potential bias built into this model. With our study, we observed a list of signs in patients from the time they were admitted to the palliative care unit. They were observed systematically, twice a day, without knowing if the patient would die or be discharged," says Hui, the study's corresponding author.

The study shows that very simple observations by doctors and care teams can help make a very important diagnosis and may inform both the patient and the family so that they can make difficult personal decisions, he explained.

For the prospective study, Hui and colleagues at MD Anderson and Barretos Cancer Hospital (an MD Anderson Sister Institution in Brazil) observed 357 cancer patients admitted to the respective palliative care units, of which 57 percent ultimately died. The researchers systematically observed 52 physical and cognitive signs -- identified by Hui and colleagues in previous research -- twice a day from the patient's admission to discharge or death. Of those 52 signs, the researchers identified the eight most highly associated with impending death within three days. Signs include:

nonreactive pupils
decreased response to verbal stimuli
decreased response to visual stimuli
inability to close eyelids
drooping of the nasolabial fold
neck hyperextension
grunting of vocal cords
upper gastrointestinal bleeding

"When cancer patients reach the last days of life, this is an extremely emotional time for families - their stress levels cannot be understated," says Hui. "Knowing when death is imminent would provide more information so caregivers can plan appropriately. For clinicians, having this information could help reassure families that we are providing the best care possible."

Hui stresses that this research is not yet practice-changing, but is an important step in understanding these eight signs and their relation to impending death. Also, says Hui, the findings are only representative of imminent cancer death and should not be generalized to other causes of death.

Follow up studies in different settings are planned: Hui and colleagues will look at the reliability of the identified signs, as well as evaluate this research in other countries and in the hospice setting.

In addition to Hui, other authors on the study include: from MD Anderson, Eduardo Bruera, M.D., professor and chair, and Swati Bansal, both of Palliative Care and Rehabilitation Medicine; and Gary Chisholm, Biostatistics. From Barretos Cancer Hospital, authors include: Renata dos Santos, M.D., and Camila Souza Crovador.