MIT: Cooperative behavior meshes with evolutionary theory

CAMBRIDGE, Mass. - One of the perplexing questions raised by evolutionary theory is how cooperative behavior, which benefits other members of a species at a cost to the individual, came to exist.

Cooperative behavior has puzzled biologists because if only the fittest survive, genes for a behavior that benefits everybody in a population should not last and cooperative behavior should die out, says Jeff Gore, a Pappalardo postdoctoral fellow in MIT's Department of Physics.

Gore is part of a team of MIT researchers that has used game theory to understand one solution yeast use to get around this problem. The team's findings, published in the April 6 online edition of Nature, indicate that if an individual can benefit even slightly by cooperating, it can survive even when surrounded by individuals that don't cooperate. In short, the study offers a concrete example of how cooperative behaviors can be compatible with evolutionary theory.

Yeast may seem unlikely subjects for a study of cooperative behavior, but in fact they are perfectly suited to such studies, says Gore. Unlike humans, yeast have no emotions or thoughts that interfere with rational decision-making; their actions are solely driven by their genetic response to the environment.

"You can apply game theory to biological interactions and in some ways it's more broadly applicable than it is in humans," says Gore, the paper's lead author.

Game theory, traditionally employed by economists and military strategists, uses mathematics to predict individuals' behavior in certain situations.

Cooperators and cheaters

Working with MIT physics professor Alexander van Oudenaarden, also an author of the paper, Gore developed an experimental setup involving yeast sucrose metabolism. Sucrose is not yeast's preferred food source, but they will metabolize it if no glucose is available. To do so, they must secrete an enzyme called invertase, which breaks sucrose into smaller sugars that the yeast can absorb.

Much of that sugar diffuses away and is freely available to other yeast cells in the environment. In this scenario, yeast that secrete invertase are known as cooperators, while those that don't secrete invertase and instead consume the simple sugars produced by others are called cheaters.

If all of these simple sugars diffused away, with no preferential access to the yeast that produced it, then it would always be better to cheat, and the cooperators would die out.

The researchers observed that cooperating yeast have preferential access to approximately 1 percent of the sucrose they produce. That benefit outweighs the cost of helping others, allowing them to successfully compete against cheaters.

In addition, no matter the initial starting numbers of yeast in a given population, the microbes always come into an equilibrium state, with both cooperators and cheaters present. "It doesn't matter where you start. You always end up with equilibrium," says Gore.

This suggests that the yeast are playing what game theorists call a snowdrift game. The name of the game comes from a situation in which two drivers are trapped in cars behind a snowdrift. Each one can choose to get out and clear a path or stay put. If one driver does not shovel, the other must.

The best option is to "cheat" by staying in the car while the other driver shovels. However, the worst-case scenario occurs if both drivers cheat and no one gets home. Therefore, the best strategy is always the opposite of your opponent's strategy.

The same rules apply to the cheating and cooperating yeast: Like the driver who grudgingly gets out and shovels so that both she and her fellow motorist - snug inside his car - may continue on their journeys, the yeast who cooperate do so because there is a slight benefit for themselves. However, when most of the yeast are cooperating, it becomes advantageous for some individuals to cheat, and vice versa, which allows co-existence between cheaters and cooperators to arise.

Studies have shown that in the wild, yeast carry different numbers of copies of the invertase gene. This genetic diversity in the wild may be similar to the long-term coexistence of cooperators and cheaters observed in the laboratory, says Gore.

Hyun Youk, an MIT graduate student in physics, is also an author of the paper. This research was funded by the National Institutes of Health and the National Science Foundation.

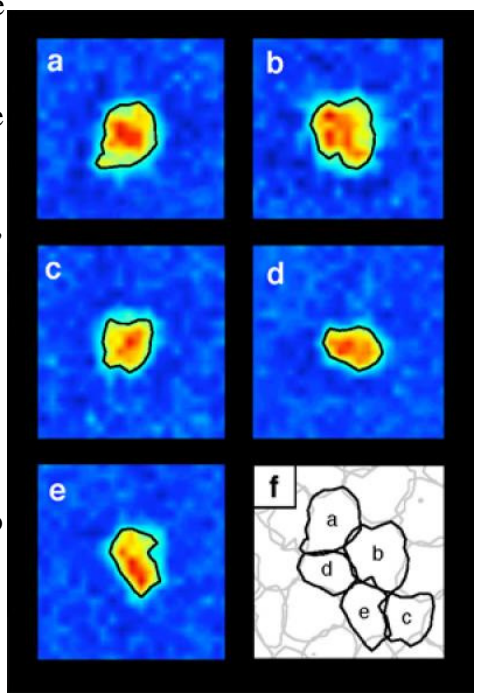
How the retina works: Like a multi-layered jigsaw puzzle of receptive fields

LA JOLLA, CA - About 1.25 million neurons in the retina - each of which views the world only through a small jagged window called a receptive field - collectively form the seamless picture we rely on to navigate our environment. Receptive fields fit together like pieces of a puzzle, preventing "blind spots" and excessive overlap that could blur our perception of the world, according to researchers at the Salk Institute for Biological Studies.

In the April 7 issue of the journal Public Library of Science, Biology, the scientists say their findings suggest that the nervous system operates with higher precision than previously appreciated and that apparent irregularities in individual cells may actually be coordinated and finely tuned to make the most of the world around us.

Previously, the observed irregularities of individual receptive fields suggested that the collective visual coverage might be uneven and irregular, potentially posing a problem for high-resolution vision. "The striking coordination we found when we examined a whole population indicated that neuronal circuits in the retina may sample the visual scene with high precision, perhaps in a manner that approaches the optimum for high-resolution vision," says senior author E.J. Chichilnisky, Ph.D., an associate professor in the Systems Neurobiology Laboratories.

All visual information reaching the brain is transmitted by retinal ganglion cells. Each of the 20 or so distinct ganglion cell types is thought to transmit a complete visual image to the brain, because the receptive fields of each type form a regular lattice covering visual space. However, within each regular lattice, the individual cells' receptive fields have irregular and inconsistent shapes, which could potentially result in patchy coverage of the visual field.



Each neuron in the retina views the world through a small, irregularly shaped window. These regions fit together like pieces of a puzzle, preventing "blind spot" and excessive overlap that could blur our perception of the world. **Image: Courtesy of Dr. Jeffrey Gauthier, Salk Institute for Biological Studies**

To understand how the visual system overcomes this problem, postdoctoral researcher and first author Jeffrey L. Gauthier, Ph.D., used a microscopic electrode array to record the activity of ganglion cells in isolated patches of retina, the tissue lining the back of the eye.

After monitoring hundreds of ganglion cells over several hours, he distinguished between different cell types based on their light response properties. "Often people record from many cells simultaneously but they don't know which cell belongs to which type," says Gauthier. Without this information, he says, he wouldn't have been able to observe that the receptive fields of neighboring cells of a specific type interlock, complementing each others' irregular shapes.

"The receptive fields of all four cell types we examined were precisely coordinated," he says, "but we saw no coordination between cells of different types, emphasizing the importance of clearly distinguishing one cell type from another when studying sensory encoding by a population of neurons."

Researchers who also contributed to the work include postdoctoral fellows Greg D. Field, Ph.D., Martin Greschner, Ph.D., and Jonathon Shlens, Ph.D., all in the Chichilnisky Laboratory, as well as postdoctoral researcher Alexander Sher, Ph.D., and professor Alan M. Litke, Ph.D., both at the Santa Cruz Institute for Particle Physics, University of California, Santa Cruz.

This work was supported by the National Institutes of Health, the National Science Foundation, the Chapman Foundation, the Helen Hay Whitney Foundation, the Burroughs Wellcome Fund, the Deutscher Akademischer Austauschdienst and the McKnight Foundation.

Evolution-proof insecticides may stall malaria forever

Killing just the older mosquitoes would be a more sustainable way of controlling malaria, according to entomologists who add that the approach may lead to evolution-proof insecticides that never become obsolete.

Each year malaria - spread through mosquito bites - kills about a million people, but many of the chemicals used to kill the insects become ineffective. Repeated exposure to an insecticide breeds a new generation of mosquitoes that are resistant to that particular insecticide.

"Insecticides sprayed on house walls or bed nets are some of the most successful ways of controlling malaria," said Andrew Read, professor of biology and entomology, Penn State. "But they work by killing the insects or denying them the human blood they turn into eggs. This imposes an enormous selection in favor of insecticide-resistant mosquitoes."

Read and his colleagues Matthew Thomas, professor of entomology, Penn State, and Penelope Lynch, doctoral student, Open University, UK, argue that insecticides - chemical or biological - that kill only older mosquitoes are a more sustainable way to fight the deadly disease.

"If we killed only older mosquitoes we could control malaria and solve the problem of resistant mosquitoes," said Read. "This could be done by changing the way we use existing insecticides, even by simply diluting them," he added.

Aging mosquitoes are easier to kill with insecticides like DDT but new generation pesticides could do it too. Read and his colleagues are working with a biopesticide that kills older mosquitoes.

"It is one of the great ironies of malaria," explained Read, whose team's findings appear today (April 7) in PLoS Biology. "Most mosquitoes do not live long enough to transmit the disease. To stop malaria, we only need to kill the old mosquitoes."

Since most mosquitoes die before they become dangerous, late-acting insecticides will not have much impact on breeding, so there is much less pressure for the mosquitoes to evolve resistance, explained Read, who is also associated with the Penn State Center for Infectious Disease Dynamics. "This means that late-life insecticides will be useful for much, much longer - maybe forever - than conventional insecticides," he added. "Insects usually have to pay a price for resistance, and if only a few older mosquitoes gain the benefits, evolutionary economics can stop resistance from ever spreading."

"We are working on a fungal pesticide that kills mosquitoes late in life," said Thomas. "We could spray it onto walls or onto treated materials such as bed nets, from where the mosquito would get infected by the fungal spores." The fungi take 10 to 12 days to kill the insects. This achieves the benefit of killing the old, dangerous mosquitoes, while dramatically reducing the selection for the evolution of resistance, Thomas explained.

To study the impact of late-acting insecticides on mosquito populations, the researchers constructed a mathematical model of malaria transmission using factors such as the egg laying cycle of the mosquito and the development of parasites within the insect.

Once malaria parasites infect a mosquito, they need at least 10 to 14 days - or two to six cycles of egg production - to mature and migrate to the insect's salivary glands. From there they can pass into humans when a mosquito bites.

Analyses of the model using data on mosquito lifespan and malaria development from hotspots in Africa and Papua New Guinea reveal that insecticides killing only mosquitoes that have completed at least four cycles of egg production reduce the number of infectious bites by about 95 percent.

Critically, the researchers also found that resistance to late-acting insecticides spreads much more slowly among mosquitoes, compared to conventional insecticides, and that in many cases, it never spreads at all.

Read says the development of biological or chemical insecticides that are more effective against older, malaria-infected mosquitoes could save the millions dollars that will have to be spent to endlessly find new insecticides to replace ones that have become ineffective.

"Insecticides that kill indiscriminately impose maximal selection for mosquitoes that render those insecticides useless. Late-life acting insecticides would avoid that fate," Read added. "Done right, a one-off investment could create a single insecticide that would solve the problem of mosquito resistance forever."

Weizmann Institute Scientists Develop a Unique Approach for Splitting Water into Hydrogen and Oxygen

The design of efficient systems for splitting water into hydrogen and oxygen, driven by sunlight is among the most important challenges facing science today, underpinning the long term potential of hydrogen as a clean, sustainable fuel. But man-made systems that exist today are very inefficient and often require additional use of sacrificial chemical agents. In this context, it is important to establish new mechanisms by which water splitting can take place.

Now, a unique approach developed by Prof. David Milstein and colleagues of the Weizmann Institute's Organic Chemistry Department, provides important steps in overcoming this challenge. During this work, the team demonstrated a new mode of bond generation between oxygen atoms and even defined the mechanism by which it takes place. In fact, it is the generation of oxygen gas by the formation of a bond between two oxygen atoms originating from water molecules that proves to be the bottleneck in the water splitting process. Their results have recently been published in Science.

Nature, by taking a different path, has evolved a very efficient process: photosynthesis – carried out by plants – the source of all oxygen on Earth. Although there has been significant progress towards the understanding of photosynthesis, just how this system functions remains unclear; vast worldwide efforts have been devoted to the development of artificial photosynthetic systems based on metal complexes that serve as catalysts, with little success. (A catalyst is a substance that is able to increase the rate of a chemical reaction without getting used up.)

The new approach that the Weizmann team has recently devised is divided into a sequence of reactions, which leads to the liberation of hydrogen and oxygen in consecutive thermal- and light-driven steps, mediated by a unique ingredient – a special metal complex that Milstein's team designed in previous studies. Moreover, the one that they designed – a metal complex of the element ruthenium – is a 'smart' complex in which the metal center and the organic part attached to it cooperate in the cleavage of the water molecule.

The team found that upon mixing this complex with water the bonds between the hydrogen and oxygen atoms break, with one hydrogen atom ending up binding to its organic part, while the remaining hydrogen and oxygen atoms (OH group) bind to its metal center.

This modified version of the complex provides the basis for the next stage of the process: the 'heat stage.' When the water solution is heated to 100 degrees C, hydrogen gas is released from the complex – a potential source of clean fuel – and another OH group is added to the metal center.

'But the most interesting part is the third 'light stage,'' says Milstein. 'When we exposed this third complex to light at room temperature, not only was oxygen gas produced, but the metal complex also reverted back to its original state, which could be recycled for use in further reactions.'

These results are even more remarkable considering that the generation of a bond between two oxygen atoms promoted by a man-made metal complex is a very rare event, and it has been unclear how it can take place. Yet Milstein and his team have also succeeded in identifying an unprecedented mechanism for such a process. Additional experiments have indicated that during the third stage, light provides the energy required to cause the two OH groups to get together to form hydrogen peroxide (H2O2), which quickly breaks up into oxygen and water. 'Because hydrogen peroxide is considered a relatively unstable molecule, scientists have always disregarded this step, deeming it implausible; but we have shown otherwise,' says Milstein. Moreover, the team has provided evidence showing that the bond between the two oxygen atoms is generated within a single molecule – not between oxygen atoms residing on separate molecules, as commonly believed – and it comes from a single metal center.

Discovery of an efficient artificial catalyst for the sunlight-driven splitting of water into oxygen and hydrogen is a major goal of renewable clean energy research. So far, Milstein's team has demonstrated a mechanism for the formation of hydrogen and oxygen from water, without the need for sacrificial chemical agents, through individual steps, using light. For their next study, they plan to combine these stages to create an efficient catalytic system, bringing those in the field of alternative energy an important step closer to realizing this goal.

Participating in the research were former postdoctoral student Stephan Kohl, Ph.D. student Leonid Schwartsburd and technician Yehoshoa Ben-David all of the Organic Chemistry Department, together with staff scientists Lev Weiner, Leonid Konstantinovski, Linda Shimon and Mark Iron of the Chemical Research Support Department.

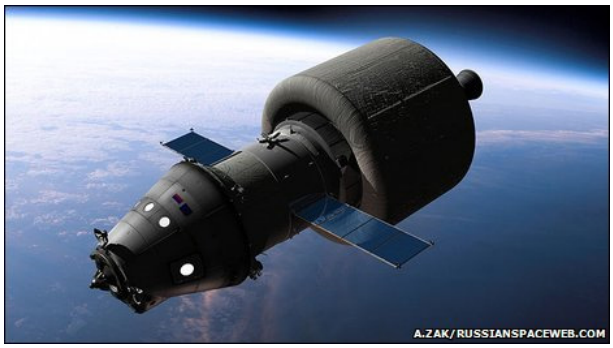
Prof. David Milstein's research is supported by the Mary and Tom Beck-Canadian Center for Alternative Energy Research; and the Helen and Martin Kimmel Center for Molecular Design. Prof. Milstein is the incumbent of the Israel Matz Professorial Chair of Organic Chemistry.

Russian rocket plans may prompt new space race

* Updated 15:50 07 April 2009 **by James Oberg**

Russia is embarking on its most ambitious space project since the heady days of the space race: planning a new spaceship, launcher and even a new launch site. The plans are remarkably similar to NASA's Orion project and could provide a vital fallback if the US, Russia or other nations run into trouble with space missions.

Until now, Russia (and formerly, the Soviet Union) has simply upgraded its existing space facilities and hardware. Its three-person Soyuz spacecraft, for example, is now in its fifth generation in 40 years. But with top-level Kremlin backing, the Russian space agency Roskosmos is planning to entirely replace its current launch facilities, the rockets used to reach orbit, and the Soyuz itself. Future launches will take place from a new site near the Pacific coast city of Vladivostok.



The new ship would be launched towards the end of the next decade

"Post-Soviet Russia has never had a massive project of this kind," boasted Aleksey Krasnov, head of the agency's human spaceflight programme in a recent press briefing.

On Monday, the agency announced that the space firm Energia would receive 800 million rubles ($24 million) to design the 20-tonne Soyuz replacement by June 2010. The first manned flight is planned for 2018.

New space race?

The craft is to carry up to six people – twice the seating of the Soyuz – or else a cargo load of 500 kilograms. It will be reusable, with up to 10 flights before retirement.

The basic design will be able to either orbit the Earth on its own or dock with the international space station, and may even be able to even repair or retrieve orbiting satellites. A beefed-up version could be capable of flights to lunar orbit and back – and perhaps beyond.

The design's suite of capabilities is similar to NASA's Orion spacecraft already under development, already earning Russia's spacecraft the tongue-in-cheek nickname "Orionski".

The Obama Administration has endorsed NASA's Bush-era plans to return astronauts to the moon, and the new craft could let Moscow achieve the same goal. This will give NASA a long-hoped-for boost in Congress by echoing the space race motivations of the 1960s.

However, the new craft will also provide a valuable lifeline for all space-faring nations. After the 2003 Columbia disaster grounded NASA's shuttle fleet for several years Soyuz provided the only way to keep the space station going. The new Russian vehicle could enhance the flexibility, effectiveness, and safety of lunar missions planned by China, Europe, Japan and India in the 2020s.

Young adults at future risk of Alzheimer's have different brain activity, says study

Young adults with a genetic variant that raises their risk of developing Alzheimer's Disease show changes in their brain activity decades before any symptoms might arise, according to a new brain imaging study by scientists from the University of Oxford and Imperial College London. The results may support the idea that the brain's memory function may gradually wear itself out in those who go on to develop Alzheimer's.

The research, published today in the journal Proceedings of the National Academy of Sciences, provides clues as to why certain people develop Alzheimer's Disease (AD) and it may be a step towards a diagnostic test that identifies individuals at risk. The degenerative condition is the most common cause of dementia and it affects around 417,000 people in the UK.

The APOE4 genetic variant is found in about a quarter of the population. Not everyone who carries the variant will go on to develop AD, but people who inherit one copy of APOE4 have up to four times the normal risk of developing the late-onset variety of the disease. People who have two copies have around ten times the normal risk.

The researchers behind today's study stress that most carriers of APOE4 will not go on to develop Alzheimer's and carriers should not be alarmed by the study's findings.

Differences in the region of the brain involved in memory, known as the hippocampus, have previously been shown in middle-aged and elderly healthy carriers of APOE4. However, the new Oxford University and Imperial study is the first to show hyperactivity in the hippocampus of healthy young carriers. It is also the first to show that APOE4 carriers' brains behave differently even at 'rest'.

The study used functional Magnetic Resonance Imaging (fMRI) carried out at the University of Oxford to compare activity inside the brains of 36 volunteers, with 18 carrying at least one copy of the APOE4 gene and 18 non-carriers acting as controls.

All the volunteers in the study were aged between 20 and 35 and all performed normally on tasks designed to test their cognitive skills.

The researchers looked at how the volunteers' brains behaved while they were resting and also while they were performing a memory-related task. Even when the APOE4 carriers were resting, the researchers could see that carriers and non-carriers each had distinct patterns of brain activity. The fMRI scans showed visible differences in how the hippocampus was relating to the rest of the brain.

The researchers will now carry out a similar study of patients with mild cognitive impairment to explore how these differences in patterns of brain activity in young people may be associated with later changes.

Dr Clare Mackay, the lead author of the study from the Department of Psychiatry and the Centre for Functional Magnetic Resonance Imaging of the Brain at the University of Oxford, said: "We have shown that brain activity is different in people with this version of the gene decades before any memory problems might develop. We've also shown that this form of fMRI, where people just lie in the scanner doing nothing, is sensitive enough to pick up these changes. These are exciting first steps towards a tantalising prospect: a simple test that will be able to distinguish who will go on to develop Alzheimer's."

Dr Christian Beckmann, another author of today's study from the Division of Neurosciences and Mental Health at Imperial College London, added: "Our brains are always active - our minds wander even when we're not carrying out specific tasks. We were surprised to see that even when the volunteers carrying APOE4 weren't being asked to do anything, you could see the memory part of the brain working harder than it was in the other volunteers. Not all APOE4 carriers go on to develop Alzheimer's, but it would make sense if in some people, the memory part of the brain effectively becomes exhausted from overwork and this contributes to the disease. This theory is supported by studies that have found the opposite pattern in people who have developed Alzheimer's, with these people showing less activity than normal in the memory part of the brain."

Hand transplants seize back lost brain territory

* 22:00 06 April 2009 **by Helen Thomson**

Hand transplants are eventually "accepted" by the brain, a study shows, raising the prospect of full movement being recovered. Surprisingly, it seems that in right-handed people, the left hand is accepted sooner.

The motor cortex – the part of the brain responsible for muscular movement – maintains a physical map of the body, with different areas registering sensations in different body parts. When the brain is deprived of sensory input from a limb, such as after a hand amputation, that region goes unused. To stop prime real estate going to waste, the brain rewires itself, with areas representing the face and upper arm "creeping in" to take over the region formerly dominated by the hand.

To find out if a transplanted hand can reclaim these brain regions, Angela Sirigu and colleagues at the Institute for Cognitive Science in Lyon, France, used magnetic pulses to stimulate these areas in two people who had undergone double hand transplants. They found that muscles in the new hands responded to the stimulation, suggesting that the brain had fully accepted them.

Previous research had shown that stroking a transplanted hand triggered brain activity in the same region as in non-amputees, but this is the first demonstration that the hand muscles are actually represented in the brain. "We can see the brain directly activating the new transplanted muscles," says Sirigu.

Head start

In both patients, the left hand was quicker to get this space back – and regain movement – than the right. In one case, the left hand re-acquired a significant "presence" in the brain after 10 months; the right hand took 26 months.

One explanation, say the researchers, is the varying flexibility of the brain regions responsible for each hand.

They believe that because both subjects were right-handed, the brain regions dominated by the right hand were more active prior to amputation and therefore not as flexible to rearrangement. In contrast, the areas corresponding to the left hand were commandeered to a greater extent by other body parts. This may have led to greater flexibility in the left-hand region, Sirigu says, allowing signals from the transplanted left hand to be integrated faster.

Amputees waiting for a transplant should still use prosthetic limbs, though. Before the transplant, both patients had prosthetics, which Sirigu believes helped to keep the original brain representation of the hand alive. "Prosthesis reduces the chronic pain experienced by patients so we can't ask them to go without," she says.

Journal reference: Proceedings of the National Academy of Sciences (DOI: 10.1073_pnas.0809614106)

Link between widely used osteoporosis drugs and heart problems probed

WINSTON-SALEM, N.C. – New research at Wake Forest University School of Medicine evaluated the link between a common class of drugs used to prevent bone fractures in osteoporosis patients and the development of irregular heartbeat.

The study's findings appear in the current issue of Drug Safety, a publication of the International Society of Pharmacovigilance covering the safe and proper use of medicines.

"Some trials show there could be a potential link between the use of bisphosphonates and the development of serious heart rhythm problems, but in our study the link wasn't conclusive," said Sonal Singh, M.D., M.P.H., an assistant professor of internal medicine and lead investigator for the study. "So we urge that additional investigations be conducted."

Bisphosphonates, found in prescription drugs including BonivaTM, FosomaxTM, ReclastTM and ActonelTM, inhibit the breakdown of bones, which reduces the risk of fractures, especially those of the spine and hips in older patients. The first such drugs were approved for use in the mid-1990s.

Early studies indicated that the use of bisphosphonates might cause problems with heart rhythm, or atrial fibrillation, which increases the risk for stroke or heart attack. For the study published this month, researchers analyzed the data from previous observational studies and clinical trials to determine the link between bisphosphonate therapy and irregular heart beat.

Researchers found that bisphosphonate use was associated with a significant increase in the incidence of "serious" heart rhythm disturbances, classified by hospitalization, disability or death resulting from the condition. However, when they included "non-serious" cases in their analysis, they found no overall increased risk of atrial fibrillation, the study shows.

"Our findings were discordant, with conflicting results," Singh said. "The challenge now is to figure out what it all means."

In the clinical trials reviewed, medical records of more than 13,000 patients who had osteoporosis or fractures and were given bisphosphonates were compared to the records of more than 13,000 patients who received a placebo during study participation. Researchers were looking for the incidence of irregular heartbeat

first, and then stroke or death caused by stroke or heart attack as a secondary outcome. The patient files reviewed were primarily of women who were treated with bisphosphonates and were generally in their early 70s, according to the study.

"We found no risk of stroke and cardiovascular mortality in the trials," Singh said. "That was very reassuring."

The observational studies evaluated the risk of irregular heartbeat in patients treated with bisphosphonates compared with those who had not received the drug. A review of these studies found different results. One study showed an increased risk of irregular heartbeat in patients taking the drugs and others showed no associated risk.

"The amount of data on the outcome of bisphosphonate use is insufficient to make a definitive conclusion," said Vinodh Jeevanantham, M.D., an instructor of internal medicine and co-researcher on the School of Medicine study.

The federal Food and Drug Administration called the results of the previous bisphosphonate studies "discordant" in a November 2008 update to its safety review of the drug. The agency's review of four previous trials also found no link between bisphosphonates and irregular heartbeat but suggested the need for more research.

Given these results, physicians should not change they way they prescribe the drugs for the majority of patients with osteoporosis, Singh said, and patients should not stop taking them. He cautioned, however, that patients with pre-existing heart conditions and those with risk factors for rhythm disturbance should be especially vigilant for the development of atrial fibrillation, and doctors should continue to closely monitor patients at risk for atrial fibrillation who are taking bisphosphonates.

"People who develop atrial fibrillation after using bisphosphonates should be reporting it to regulatory agencies," Singh said.

Yoon K. Loke, M.D., MBBS, of the University of East Anglia, Norwich, United Kingdom, also participated in this study, which received no external funding.

Acupuncture 'probably ineffective' in treatment of hot flushes

Acupuncture cannot be shown to have any positive effect on hot flushes during the menopause. This is the conclusion of a systematic review of literature by three groups in Daejon, Busan (South Korea) and Exeter (UK), published in the current edition of the peer-reviewed journal Climacteric.

Many women are concerned by the unfavourable publicity given to HRT use, but still have to deal with the symptoms which can occur during and after the menopause. A significant minority of women look for alternatives to HRT to deal with these symptoms. Often these alternatives are untested, and it can be impossible to balance the risks and benefits of these treatments against the risks and benefits of conventional treatments or the discomfort of untreated menopause.

The researchers reviewed studies on the use of acupuncture for the relief of hot flushes during the menopause. They identified 106 studies in total, which they eventually narrowed down to the six most relevant to the study. These six studies were randomised controlled trials (RCTs), which included testing the effects of real acupuncture against the effect of sham acupuncture. Only one RCT reported favorable effect of acupuncture on the frequency and severity of hot flush after 4 weeks follow-up, while the other five RCTs demonstrated no such effects.

Researchers caution that the quality of good studies is not great, and that because of this the use of acupuncture cannot be completely ruled out. However, the available literature indicates that acupuncture does not seem to be effective in the treatment of menopausal hot flushes.

Lead researcher, Dr Myeong Soo Lee (Korea Institute of Oriental Medicine, South Korea) said

Although the availability of good Randomised Controlled Trials is too small to draw any firm conclusion, in general the evidence from sham-controlled RCTs for the effects of acupuncture for treating menopausal hot flush is not convincing. We would always recommend that women wanting relief from menopausal symptoms consult their clinician before undertaking any course of treatment.

Commenting, Dr David Sturdee (President of the International Menopause Society) said:

There's no doubt that many women need relief from the symptoms associated with the menopause. They need to make sure that the treatment they choose works, and is right for them. I would always recommend that a woman consult her clinician before starting any treatment.

Earthshine reflects Earth's oceans and continents from the dark side of the Moon

Researchers from the University of Melbourne and Princeton University have shown for the first time that the difference in reflection of light from the Earth's land masses and oceans can be seen on the dark side of the moon, a phenomenon known as earthshine.

The paper is published in this week's edition of the international journal Astrobiology.

Sally Langford from the University of Melbourne's School of Physics who conducted the study as part of her PhD, says that the brightness of the reflected earthshine varied as the Earth rotated, revealing the difference between the intense mirror-like reflections of the ocean compared to the dimmer land.

"In the future, astronomers hope to find planets like the Earth around other stars. However these planets will be too small to allow an image to be made of their surface," she said. "We can use earthshine, together with our knowledge of the Earth's surface to help interpret the physical make up of new planets."

This is the first study in the world to use the reflection of the Earth to measure the effect of continents and oceans on the apparent brightness of a planet. Other studies have used a colour spectrum and infrared sensors to identify vegetation, or for climate monitoring.

The three year study involved taking images of the Moon to measure the earth's brightness as it rotated, allowing Ms Langford to detect the difference in signal from land and water.

Observations of the Moon were made from Mount Macedon in Victoria, for around three days each month when the Moon was rising or setting. The study was conducted so that in the evening, when the Moon was a waxing crescent, the reflected earthshine originated from Indian Ocean and Africa's east coast. In the morning, when the Moon was a waning crescent – it originated only from the Pacific Ocean.

"When we observe earthshine from the Moon in the early evening we see the bright reflection from the Indian Ocean, then as the Earth rotates the continent of Africa blocks this reflection, and the Moon becomes darker," Ms Langford said. "If we find Earth sized planets and watch their brightness as they rotate, we will be able to assess properties like the existence of land and oceans."

Has HIV Become More Virulent?

Damage to patients' immune systems is happening sooner now than it did at the beginning of the HIV epidemic, suggesting the virus has become more virulent, according to a new study in the May 1, 2009 issue of Clinical Infectious Diseases, now available online.

Conventional wisdom says several years will pass between HIV infection and the need for antiretroviral therapy. However, clinicians have observed that patients are entering HIV care with lower initial CD4 cell counts than in previous years and now often require antiretroviral therapy soon after entering care, raising the question of whether HIV has become more virulent.

Researchers studied data from more than 2,000 HIV-positive active-duty military personnel, retirees, and dependents between 1985 and 2007 who had tested HIV-negative within the previous four years. When they looked at patients' first CD4 count after HIV diagnosis, they found that it decreased from an average of 632 cells/mm³ in 1985-1990 to 514 cells/mm³ in 2002-2007. Additionally, 25 percent of patients diagnosed with HIV in recent years already had fewer than 350 CD4 cells/mm3, the threshold for when antiretroviral therapy should begin, compared to only 12 percent of patients in the late 1980s.

The authors note that the trend seems to have stabilized, perhaps due to the widespread introduction of highly active combination antiretroviral therapy.

This is the first study from the United States which shows that the immune cells among recently diagnosed HIV patients has dramatically fallen during the HIV epidemic. These findings are similar to those found in the study from Europe, which suggests that these trends may be widespread.

"Unfortunately, it may no longer be true that there is a time period of several years between diagnosis and the need for treatment – instead this time-span is shortening" said study author Nancy Crum-Cianflone MD, of the San Diego Naval Medical Center. "Early diagnosis is important for several reasons including that patients can enter into medical care and begin treatment before the immune system becomes weak and opportunistic infections develop."

VA/UAB Study Looks at Functional Decline in Older Patients After Hospitalization

• Hospitalization causes functional decline in older adults.

• Surgical patients regain more function than non-surgical patients.

• Suggests changes in management of hospitalized seniors.

BIRMINGHAM, Ala. - Motivation and expectation may be factors in helping older adults regain lost functional ability after hospitalization, say researchers with the Birmingham Veterans Administration Medical Center and UAB (University of Alabama at Birmingham). In findings published in March in the Annals of Internal Medicine, researchers found that patients hospitalized for surgery returned to normal baseline function more quickly and more completely than did patients hospitalized for illness.

Researchers used UAB's Study of Aging Life-Space Assessment, a measure of mobility developed at UAB's Center for Aging, to determine the functional level of seniors before and after hospitalization. On average, patients hospitalized for surgery had a sharp decline in life-space scores immediately after surgery, but returned

to or exceeded pre-surgical scores within one year. Patients hospitalized for illness or other medical reasons experienced a lower post-hospitalization decline but did not return to pre-hospitalization scores, experiencing a marked functional decline following hospitalization even after two years.

"The difference may be caused by the presence of increased expectations of recovery and increased motivation in patients presenting for surgery," said Cynthia Brown, M.D., an investigator with the VA's Geriatric Research, Education and Clinical Center and assistant professor in UAB's Division of Gerontology, Geriatrics and Palliative Care. "Patients who undergo surgery expect their medical condition to be fixed and thus to be able to function as well as or better than before. Our analysis indicates that, by and large, that occurs."

The problem, said Brown, are the non-surgical older patients hospitalized for medical issues such as pneumonia or heart disease. The findings show this group on average does not return to baseline, but experiences a permanent decline in their level of mobility.

One hypothesis is that there is no real expectation of full recovery of function by the patient, family or health care providers. Additionally, patients tend to remain immobile in a hospital bed during their stay and may have multiple ailments that complicate treatment. Increased medication also may promote confusion and depression.

"All of these factors can start patients down a slippery slope of functional decline," said Brown. "Our findings suggest that surgical patients return to function, those hospitalized for illness do not. We need to look at our hospital culture to understand why that happens, and to develop interventions to prevent that decline."

Brown said concepts such as Acute Care for Elders (ACE) units, which use patient-centered care, discharge planning, medication review and a specialized environment have shown promise in reducing the decline. Efforts to boost physical and cognitive activity should also be examined.

"Mental status and physical function are targets for intervention during hospitalization," she said. "We need to see about getting these patients up and out of their hospital beds. If we can get these people up faster, perhaps we can reduce hospitalization stays and reduce the risk of falls."

The Life-Space Assessment, developed by Richard Allman, M.D., and Patricia Baker, Ph.D., of UAB's Center for Aging, measures an individual's mobility and degree of independence. Life-space is based upon the distance a person routinely travels to perform activities. The Life-Space Assessment measures how often a person leaves his or her residence, the distance from the residence traveled and how much assistance is needed from other individuals or from assistive devices.

"It is a measure of community mobility and participation in everyday life," Brown said. "Can the individual go to church, go out to dinner, and go to the doctor's office. A life-space decrease may result in a decrease in the distance and frequency of travel from home, thus limiting participation in society. Mobility is a core function that reflects the lifestyle of community-dwelling adults and is an important predictor of morbidity and mortality." *Primary funding for the study came from the National Institute on Aging.*

Schizophrenics see through hollow-mask illusion

* 14:01 07 April 2009 **by Sandrine Ceurstemont**

Telling the front from the back of a mask can be more difficult than it seems. Thanks to an effect called the hollow-mask illusion, the brain can have trouble deciding if the image is convex or concave.

But, it seems, not everyone struggles to correctly determine the mask's orientation. New research shows that people with schizophrenia are immune to the effect – a finding that means the illusion could provide a diagnostic test for the condition.

In the study, volunteers were monitored in an fMRI (functional Magnetic Resonance Imaging) scanner as they looked at photos. Some of these were normal pictures of faces, but others had been inverted as in the hollow-mask illusion. All the participants with schizophrenia could distinguish between the two types of photos, whereas control volunteers without the condition were fooled 99 per cent of the time.

Video: ***See the hollow-mask illusion***

People with schizophrenia, which affects about 1 per cent of the population, are already known to be immune to certain visual illusions. Immunity to the hollow-mask illusion, says Danai Dima, of Hannover School of Medicine in Germany, suggests that the "bottom-up" process of collecting incoming visual information from the eyes, and the "top-down" process of interpreting this information is different in people with schizophrenia.

"The term 'schizophrenia' was coined almost a century ago to mean the splitting of different mental domains, but the idea has now shifted more towards connectivity between brain areas," says Dima.

The prevailing theory is that perception comprises three main components: sensory input (bottom-up); the internal production of concepts (top-down); and a control component, which covers interaction between the two first components. "Our study provides further evidence of 'dysconnectivity' between these components in the brains of people with schizophrenia." *Journal reference: NeuroImage (DOI: 10.1016/j.neuroimage.2009.03.033)*

Ebola accident puts vaccine to the test

* 14:34 07 April 2009 **by Debora MacKenzie**

Did an experimental vaccine save a scientist in Germany from Ebola? The lives of others who work with the deadly virus might ride on the answer.

On 12 March a woman working at the Bernhard Nocht Institute for Tropical Medicine (BNI) in Hamburg accidentally pricked her finger with a needle carrying Ebola virus.

There is no approved vaccine for Ebola, and such injuries have killed lab workers before. So she was given an experimental vaccine consisting of a live vesicular stomatitis virus (VSV) carrying an Ebola protein.

Still healthy

The vaccine was being developed by scientists in Canada and the US mainly to protect lab workers. She has so far developed no symptoms, and doctors now think she is unlikely to.

But was it because the vaccine worked, or because she didn't receive enough virus to cause an infection? It should be possible to tell. A vaccine would only prompt the production of antibodies to the one Ebola protein it carries. Infection would produce antibodies to many different Ebola proteins.

Stephan Günther, head of virology at the BNI, says the woman has very low levels of antibodies. These might be caused by the vaccine: when it was tested on monkeys it elicited only low levels of antibodies, but they were enough to protect the animals from Ebola. "We don't know if this might also result from a mild infection," Günther says.

Messy brew

The vaccine given to the woman was not a cleaned-up, commercial preparation but an experimental brew that also had proteins from the cultures where it was grown. As a result, she is making antibodies to those as well as to Ebola.

It takes very sensitive tests to pick out and characterise the Ebola antibodies. Because the BNI is not developing Ebola vaccine it has no such tests. It may send samples to the US Army Medical Research Institute of Infectious Diseases in Maryland, which does have suitable tests.

Ebola scientists would welcome evidence that the vaccine was safe and effective, but because the woman is now recovering there may not be money to pursue the investigation. If a vaccine company cares to develop it further, "Ebola researchers could volunteer for the safety tests", says Günther – and become immunised.

House Dust Yields Clue to Asthma: Roaches

By ELISSA ELY, M.D

Asthma is the most common chronic disease of childhood, one that strikes the poor disproportionately. Up to one-third of children living in inner-city public housing have allergic asthma, in which a specific allergen sets off a cascade of events that cause characteristic inflammation, airway constriction and wheezing.

Now, using an experimental model that required leaving the pristine conditions of the lab for the messier ones of life, a team of scientists from the Boston University School of Medicine have discovered what that allergen is.

For inner-city children," said the lead researcher, Dr. Daniel G. Remick, a professor of pathology, "the major cause of asthma is not dust mites, not dog dander, not outdoor air pollen. It's allergies to cockroaches."

Dr. Remick and his colleagues (then at the University of Michigan) published their first paper in 2002, after developing their model over several years. Their laboratory was in Detroit, where, as in many other cities, public housing suffered from pest infestation. The team made home visits with an old-time data-collection instrument: the vacuum cleaner.

"We collected house dust - big dust bunnies - added water, let them mix overnight, and spun the junk out of them, until we had extract," said Dr. Remick, now 56.

The extract was filled with proteins from Blattella germanica - the common cockroach - whose exoskeletons and droppings become airborne after death. Back in the laboratory, mice were exposed to the dust bunny particles. After being injected, they were immunologically primed: their cellular response systems went on alert.

When exposed to the same particles a second time by inhaling them, the systems on alert went to attack. Mice that had been breathing easily had difficulty exhaling, and their respiration slowed - a rodent corollary to wheezing. They were having asthma attacks.

Analysis of their lungs showed that their airways were clogged with white blood cells, mostly of a type called eosinophils, that caused mucus secretion, tissue damage and changes in muscle contractibility. Mice in a control

group, exposed to dust mites instead of cockroach protein, had none of the same respiratory or pathologic changes. The team reproduced their results in several sites; different dust bunnies, same allergic reaction.

"We're pretty excited," Dr. Remick said in an interview, "because this is the first time someone has actually taken stuff from houses where kids have asthma."

Researchers not directly involved with the studies said they were excited, too. "It's a clever thing," said Dr. Lester Kobzik, a pathology professor at Harvard Medical School. "He's collected the nasty material people actually get allergic to. "You can't call up your chemical supplier of scientific reagents and say, 'I would like five pounds of exactly the same house dust,' " Dr. Kobzik continued. "Remick had a bucketload, so he could do several years' worth of experimentation and study it carefully."

Dr. Peter A. Ward, a professor of pathology at the University of Michigan Health Services, who recruited Dr. Remick into residency almost 25 years ago, called the work "probably the closest thing in animal models to simulating what one sees in human asthma."

Most laboratory asthma research still uses genetically created proteins to induce symptoms in mice; often, the proteins are taken from egg whites. This is scientifically pleasing, but less relevant to real life. Egg whites (which humans rarely grow allergic to) have little in common with the city dust children are more likely to cavort through and inhale.

Using the same mouse model, Dr. Remick is now studying the effects of various asthma treatments, including the anti-inflammatory drugs called tumor necrosis factor inhibitors, like Remicade and Enbrel. The drugs, already used for treating rheumatoid arthritis and inflammatory bowel disease, appear to derail a crucial immunologic compound that attracts eosinophils.

"Blocking tumor necrosis factor in a mouse model improves asthma," Dr. Remick said. "It's pretty slick."

And a more exotic strategy is also under investigation. A few years ago, when Dr. Remick's colleague Jiyoun Kim presented results of the mouse model at a professional conference in Korea, an audience member asked whether he had heard about standard Chinese herbal treatment. He took herb samples back to the United States, and in mice they proved to block eotaxin, the compound that sets off asthmatic reactions.

Chinese herbs carry the whiff and romance of an easy solution without the rigors of federal drug trials. But Dr. Remick warns that caution is in order. "The power and trouble with Chinese herbal medicines," he said, "is that they have more than one active ingredient - they have dozens. We know they block eotaxin, but we don't know everything they block, or what actually makes things better."

Complicating the treatment is the disease; asthma has many mechanisms. "There may be 50 different inflammatory processes going on," Dr. Remick went on. "We're still in the process of precisely defining which part of the herbs block which part of the inflammatory response."

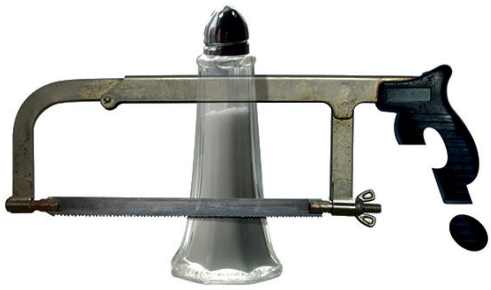
Still, hopeful parents, attracted by herbal treatments, have caused the researchers some anxious moments. "Yesterday," Dr. Remick said, "I was contacted by someone whose co-worker wanted to know whether she should use Chinese herbs to treat her daughter's asthma. I immediately replied that she shouldn't. It's not a question of Eastern versus Western medicine. Other drugs that treat asthma are better defined at this point. Herbs shouldn't be front-line. If my child had asthma," he added, "I'd take her to the pediatrician."

Findings

Public Policy That Makes Test Subjects of Us All

By JOHN TIERNEY

Suppose you wanted to test the effects of halving the amount of salt in people's diets. If you were an academic researcher, you'd have to persuade your institutional review board that you had considered the risks and obtained informed consent from the participants.



Viktor Koen

You might, for instance, take note of a recent clinical trial in which heart patients put on a restricted-sodium diet fared worse than those on a normal diet. In light of new research suggesting that eating salt improves mood and combats depression, you might be alert for psychological effects of the new diet. You might worry that people would react to less-salty food by eating more of it, a trend you could monitor by comparing them with a control group.

But if you are the mayor of New York, no such constraints apply. You can simply announce, as Michael Bloomberg did, that the city is starting a "nationwide initiative" to pressure the food industry and restaurant chains to cut salt intake by half over the next decade. Why bother with consent forms when you can automatically enroll everyone in the experiment?

And why bother with a control group when you already know the experiment's outcome? The city's health commissioner, Thomas R. Frieden, has enumerated the results. If the food industry follows the city's wishes, the health department's Web site announces, "that action will lower health care costs and prevent 150,000 premature deaths every year."

But that prediction is based on an estimate based on extrapolations based on assumptions that have yet to be demonstrated despite a half-century of efforts. No one knows how people would react to less-salty food, much less what would happen to their health.

Dr. Frieden has justified the new policy by pointing to the "compelling evidence" for the link between salt and blood pressure. It's true that lowering salt has been shown to lower blood pressure on average, but that doesn't mean it has been demonstrated to improve your health, for a couple of reasons.

First, a reduced-salt diet doesn't lower everyone's blood pressure. Some individuals' blood pressure can actually rise in response to less salt, and most people aren't affected much either way. The more notable drop in blood pressure tends to occur in some - but by no means all - people with hypertension, a condition that affects more than a quarter of American adults.

Second, even though lower blood pressure correlates with less heart disease, scientists haven't demonstrated that eating less salt leads to better health and longer life. The results from observational studies have too often been inconclusive and contradictory. After reviewing the literature for the Cochrane Collaboration in 2003, researchers from Copenhagen University concluded that "there is little evidence for long-term benefit from reducing salt intake."

A similar conclusion was reached in 2006 by Norman K. Hollenberg of Harvard Medical School. While it might make sense for some individuals to change their diets, he wrote, "the available evidence shows that the influence of salt intake is too inconsistent and generally too small to mandate policy decisions at the community level."

In the past year, researchers led by Salvatore Paterna of the University of Palermo have reported one of the most rigorous experiments so far: a randomized clinical trial of heart patients who were put on different diets. Those on a low-sodium diet were more likely to be rehospitalized and to die, results that prompted the researchers to ask, "Is sodium an old enemy or a new friend?"

Those results, while hardly a reason for you to start eating more salt, are a reminder that salt affects a great deal more than blood pressure. Lowering it can cause problems with blood flow to the kidneys and insulin resistance, which can increase the risk of strokes and heart attacks.

Salt deprivation might also darken your mood, according to recent research by Alan Kim Johnson and colleagues at the University of Iowa. After analyzing the behavior and brain chemistry of salt-deprived rats, the psychologists found that salt, like chocolate and cocaine, affected reward circuitry in the brain, and that salt-deprived rats exhibited anhedonia, a symptom of depression characterized by the inability to enjoy normally pleasurable activities.

Dr. Frieden has predicted that people "won't notice the difference" if salt is gradually reduced, but how can he be sure? What if they respond by eating more food, or a different mix of foods and stimulants? What if the food industry turns to salt substitutes that cause new health problems? "We have no way of knowing the health effects of eating less salt, yet we're supposed to forge ahead with this new policy that affects the whole population," said Michael Alderman, an expert in hypertension at the Albert Einstein College of Medicine. Like other critics, he has compared the antisalt campaign to the campaign against fat that began several decades ago.

That antifat campaign, like the antisalt campaign, was endorsed by prominent groups and federal agencies before the campaigners' theory was tested in rigorous trials. It too seemed quite logical - in theory.

But in practice the results were dismal, as demonstrated eventually by clinical trials and by the expanding waistlines of Americans. People followed the advice in the "food pyramid" to reduce the percentage of fat in the diet, but they got more obese, perhaps because they ate so many other ingredients in foods with "low fat" labels.

You might think that experience would inspire caution among public health officials, but instead they seem to be gaining confidence. When Dr. Frieden and Mr. Bloomberg decided several years ago that trans fats were dangerous, they didn't simply issue a warning or a set of voluntary guidelines. They insisted on outlawing trans fats in New York's restaurants.

At the time, it seemed extraordinary for a city to be forbidding its diners to order a legal food product, particularly given the scientific uncertainties about trans fats and the possible harms resulting from the ban (see TierneyLab at nytimes.com/tierneylab).

But that local restaurant policy now seems fairly modest by comparison with Mr. Bloomberg's and Dr. Frieden's plans for salt. Soon, wherever you live, wherever you eat, you could be part of their experiment.

Did a nickel famine trigger the 'Great Oxidation Event'?

Washington, D.C.- The Earth's original atmosphere held very little oxygen. This began to change around 2.4 billion years ago when oxygen levels increased dramatically during what scientists call the "Great Oxidation Event." The cause of this event has puzzled scientists, but researchers writing in Nature* have found indications in ancient sedimentary rocks that it may have been linked to a drop in the level of dissolved nickel in seawater.

"The Great Oxidation Event is what irreversibly changed surface environments on Earth and ultimately made advanced life possible," says research team member Dominic Papineau of the Carnegie Institution's Geophysical Laboratory. "It was a major turning point in the evolution of our planet, and we are getting closer to understanding how it occurred."

The researchers, led by Kurt Konhauser of the University of Alberta in Edmonton, analyzed the trace element composition of sedimentary rocks known as banded-iron formations, or BIFs, from dozens of different localities around the world, ranging in age from 3,800 to 550 million years. Banded iron formations are unique, water-laid deposits often found in extremely old rock strata that formed before the atmosphere or oceans contained abundant oxygen. As their name implies, they are made of alternating bands of iron and silicate minerals. They also contain minor amounts of nickel and other trace elements.

Nickel exists in today's oceans in trace amounts, but was up to 400 times more abundant in the Earth's primordial oceans. Methane-producing microorganisms, called methanogens, thrive in such environments, and the methane they released to the atmosphere might have prevented the buildup of oxygen gas, which would have reacted with the methane to produce carbon dioxide and water. A drop in nickel concentration would have led to a "nickel famine" for the methanogens, who rely on nickel-based enzymes for key metabolic processes. Algae and other organisms that release oxygen during photosynthesis use different enzymes, and so would have been less affected by the nickel famine. As a result, atmospheric methane would have declined, and the conditions for the rise of oxygen would have been set in place.

The researchers found that nickel levels in the BIFs began dropping around 2.7 billion years ago and by 2.5 billion years ago was about half its earlier value. "The timing fits very well. The drop in nickel could have set the stage for the Great Oxidation Event," says Papineau. "And from what we know about living methanogens, lower levels of nickel would have severely cut back methane production."

What caused the drop in nickel? The researchers point to geologic changes that were occurring during the interval. During earlier phases of the Earth's history, while its mantle was extremely hot, lavas from volcanic eruptions would have been relatively high in nickel. Erosion would have washed the nickel into the sea, keeping levels high. But as the mantle cooled, and the chemistry of lavas changed, volcanoes spewed out less nickel, and less would have found its way to the sea.

"The nickel connection was not something anyone had considered before," says Papineau. "It's just a trace element in seawater, but our study indicates that it may have had a huge impact on the Earth's environment and on the history of life."

Dominic Papineau's research is supported by the NASA Exobiology and Evolutionary Biology Program and from the Fond québécois de la recherche sur la nature et les technologies.

**Kurt O. Konhauser, Ernesto Pecoits, Stefan V. Lalonde, Dominic Papineau, Euan G. Nisbet, Mark E. Barley, Nicholas T. Arndt, Kevin Zahnle & Balz S. Kamber, Oceanic nickel depletion and a methanogen famine before the Great Oxidation Event, scheduled for publication in Nature on 09 April, 2009.*

Joslin study identifies 'good' energy burning fat in lean adults

Finding may lead to treatments for obesity, diabetes

BOSTON – Researchers at the Joslin Diabetes Center have demonstrated that adult humans still have a type of "good" fat previously believed to be present only in babies and children. Unlike white fat, which stores energy and comprises most body fat, this good fat, called brown fat, is active in burning calories and using energy. The finding, reported in the April 9th issue of The New England Journal of Medicine, could pave the way for new treatments both for obesity and type 2 diabetes.

Scientists had thought that brown fat only existed in humans during childhood and was mostly gone by adulthood. The paper shows that brown fat not only exists in adult humans, but also for the first time, that the fat is metabolically active.

"The fact that there is active brown fat in adult humans means this is now a new and important target for the treatment of obesity and type 2 diabetes," said C. Ronald Kahn, M.D., senior author and Head of the Joslin Section on Obesity and Hormone Action and the Mary K. Iacocca Professor of Medicine at Harvard Medical School.

Obesity is a major risk factor for type 2 diabetes. According to the researchers, the idea behind a new therapy would be to find a way to stimulate brown fat growth to both control weight and improve glucose metabolism.

"Not only did we find active brown fat in adult humans, we found important differences in the amount of brown fat based on a variety of factors such as age, glucose levels and, most importantly, level of obesity," said lead author Aaron Cypess, M.D., Ph.D., a Research Associate and Staff Physician at Joslin.

Not surprisingly, the study found that younger patients were more likely to have larger amounts of brown fat, and the brown fat was more active during colder weather, keeping with its role of burning energy to generate heat. Brown fat was also more common in adults who were thin and had normal blood glucose levels.

"What is of particular interest is that individuals who were overweight or obese as measured by higher Body Mass Index (BMI) were less likely to have substantial amounts of brown fat," said Kahn. "Likewise, patients taking beta-blockers and patients who were older were also less likely to have active brown fat. For example, individuals both over age 64 and with high BMI scores were six times less likely to have substantial amounts of brown fat."

The findings, particularly those having to do with BMI, suggest a potential role for brown fat in regulating body weight metabolism, the paper says, suggesting that higher levels of brown fat may protect against age-related obesity.

According to the paper, the researchers are hopeful that an increased ability to measure brown fat mass and activity in vivo in humans will lead to a better understanding of its role in physiology and its potential as a target for therapy of obesity and other metabolic disorders.

This study answered those questions thanks to the use of modern imaging technology.

The researchers analyzed a database of 1,972 patients who had undergone positron emission tomography/computed tomography (PET/CT) scans for a variety of reasons over a three-year period. They identified substantial brown fat deposits in 7.5 percent of the female patients and over 3 percent of males.

"These numbers clearly represent an underestimate, since PET/CT can only detect collections of brown fat cells of a certain size and activity, and could miss smaller and less active deposits," Kahn explained.

In addition, the researchers identified 33 other patients whose pathology records had indicated the presence of brown fat in their necks in the same places where the PET/CT scans had identified the largest concentrations of brown fat. They tested the tissue of two of those patients and detected the presence of a special heat-generating protein called UCP-1 that is unique to brown fat. "These findings suggest that there is previously unrecognized, heat-generating brown fat in many adults," Dr. Cypess said.

"This study, by demonstrating the presence and physiological activity of brown fat in adult humans, shows that this tissue may provide a novel and valuable target for interventions, pharmacological and environmental, to modulate energy expenditure," said Francesco Celi, M.D., of the Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, who wrote an accompanying editorial but was not involved in the Joslin study.

Dr. Kahn said there is a good possibility that brown fat may be present in significant amounts in much higher percent of the population, but that it may be more spread out and not as easily seen on imaging in many cases. Most of the deposits found on the scans were located in the neck region.

"In the real world, there has been a long debate as to whether brown fat exists in adult humans and whether it was important physiologically," he said. "This study demonstrates that it is both present and appears to be physiologically important in terms of body weight and glucose metabolism. We hope this opens up a new therapeutic area for obesity and type 2 diabetes by modifying the activity of brown fat."

In a study published in August 2008, Dr. Kahn and others showed that a protein, BMP-7, known for its role in inducing bone growth, can also help promote the development of brown fat in rodents. And, a 2007 study led by Dr. Kahn found clusters of brown fat cells dispersed between bundles of muscle fibers in strains of mice resistant to obesity and diabetes.

The current study was supported by the Clinical Investigator Training Program, Beth Israel Deaconess Medical Center - Harvard/MIT Health Sciences and Technology, in collaboration with Pfizer Inc. and Merck & Co.; as well as with grants from the National Institutes of Health and the Eli Lilly Foundation.

Others participating in the research were Allison B. Goldfine, M.D., Yu-Hua Tseng and Alessandro Doria, M.D., all of the Joslin Diabetes Center Research Division; Sanaz Lehman, M.B., B.S., Gethin Williams, M.B., B.S., Ph.D., Ilan Tal, Ph.D., and Dean Rodman, M.D., all of the Division of Nuclear Medicine, Beth Israel Deaconess Medical Center; Frank C. Kuo, M.D., of the Department of Pathology, Brigham and Women's Hospital; and Edwin L. Palmer, M.D., of the Division of Nuclear Medicine, Massachusetts General Hospital.

Soybean component reduces menopause effects

Soy aglycons of isoflavone (SAI), a group of soybean constituent chemicals, have been shown to promote health in a rat model of the menopause. The research, described in BioMed Central's open access journal Nutrition & Metabolism, shows how dietary supplementation with SAI lowers cholesterol, increases the anti-oxidative properties of the liver and prevents degeneration of the vaginal lining.

Robin Chiou led a team of researchers from National Chiayi University, Taiwan, who studied the effects of the dietary supplement on a group of female rats that had undergone ovary removal. He said, "These ovariectomized animals are a good model for study of the menopause as the loss of oestrogen from the ovaries mimics the natural reduction in oestrogen seen in menopausal women. SAI itself has weak oestrogenic properties and we've shown here that menopause-related syndromes can be prevented or improved by dietary supplementation with the compounds it contains".

In comparison to control animals, the authors found that the ovariectomized rats fed a diet enriched with SAI showed increased liver antioxidative activities and improved lipid profiles. Levels of harmful LDL cholesterol were reduced, while beneficial HDL cholesterol was increased. According to Chiou, "It is generally agreed that the higher HDL and the lower LDL concentrations are of benefit in chemoprevention of cardiovascular diseases. Our findings support the indication that soybean consumption may prevent coronary heart disease".

The authors hope that dietary soy supplementation may provide an alternative to hormone replacement therapy (HRT), which has been linked to the development of uterus and breast cancers.

Notes to Editors

1. Supplementary health benefits of soy aglycons of isoflavone by improvement of serum biochemical attributes, enhancement of liver antioxidative capacities and protection of vaginal epithelium of ovariectomized rats
Tu-Fa Lien, Yu-Lin Hsu, Dan-Yuan Lo and Robin Y.-Y. Chiou Nutrition & Metabolism (in press)
During embargo, article available here:
http://www.nutritionandmetabolism.com/imedia/1043102337244264_article.pdf?random=125465

Meat now, sex later for Ivorian chimps

* 01:00 08 April 2009 **by Ewen Callaway**

Chimpanzees trade precious scraps of meat for sex, new research shows. A two-year study of wild chimps finds that males boost their chances of having sex with a female by offering her meat.

But don't call them prostitutes. "It's not like 'I give you meat and a few hours later you're going to copulate with me,'" says Cristina Gomes, a primatologist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

She and colleague Christophe Boesch instead uncovered more nuanced and long-term exchanges.

This could be why others who have studied meat-for-sex trades between chimpanzees turned up equivocal or negative results, Gomes says. Previous studies found that males are just as likely to share meat with sexually active, oestrous females as with non-oestrous females, who don't have sex. Males, also, seem no more eager to hunt or share meat when females are likely to get pregnant.

However, Gomes previously found that chimpanzees in Ivory Coast's Taï National Park exchange back scratches over a long period of time, and wondered whether meat-for-sex trades aren't so immediate either.

Isha, an adult female wild chimpanzee, holding a piece of meat (the foot of a black and white colobus monkey) that she received from an adult male chimpanzee **(Image: Cristina M. Gomes)**

Whimpering pleas

To make this case, her team recorded meat-sharing over 22 months, noting who gave meat to whom. After a successful monkey hunt females tended to surround a male hunter and make whimpering pleas. In some cases, the male handed meat to a female, but more often than not he simply allowed her access to the carcass. The male with the meat decides who gets it, Gomes says.

Separately, she spent a total of 3000 hours following individual chimps from dawn to dusk, noting who mated with whom. After crunching all this data, she and Boesch found clear evidence pointing to meat-for-sex exchanges. On average, males who shared meat with a specific female were twice as likely to mate with her, compared to a less generous male, they found.

Whether a female was in oestrous or not when they received meat didn't seem to make much of a difference. When Gomes' team analysed only meat-sharing with females who couldn't get pregnant, the meat-for-sex relationship remained clear. "That means that it's not a short-term thing," she says.

Her team's analysis did not determine how long it took for these exchanges to even out. Nor could they tell if males who share extra meat get even more sex than males who share less.

Gomes also isn't sure if all chimpanzees exchange meat for sex. In Gombe National Park in Tanzania, for instance, males tend to be more coercive than at Taï National Park. "If males are just forcing females to copulate with them, they don't need to share meat," Gomes says.

Female chimpanzees at Gombe still get meat, says Ian Gilby, a Harvard University anthropologist who studies hunting and meat-sharing in the park. However Gombe females are more direct in their demands, often snatching at the carcass and putting their hands in front of a male's mouth to prevent him from eating. Such persistence could explain meat-sharing instead of sex trades, he says.

Still, Gilby says the new work will "liven the debate over whether chimpanzees trade meat-for-sex."

Human parallels

Even if meat-for-sex trades aren't the rule in all chimpanzee communities, the exchanges may help understand why, in some human cultures, the best male hunters father the most children, Gomes says. Anthropologists have suggested that women prefer higher-status men and that children of the best hunters get better treatment and are more likely to survive, but Gomes wonders if meat-for-sex trades might also play a role.

"We have to go back and study humans more carefully and try to see if we can determine if they exchange meat for sex," she says. *Journal reference: PLoS One (DOI: 10.1371/journal.pone.0005116)*

Traditional Media Provide More Comprehensive News Than Citizen Media and Blogs, MU Researchers Find

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COLUMBIA, Mo. –Researchers from the University of Missouri School of Journalism recently completed a comprehensive comparison of citizen journalism sites (news sites and blogs) and traditional media Web sites. They found that despite ongoing reports of financial troubles and cutbacks, legacy media are more comprehensive and more technologically advanced than citizen media and bloggers.

"We found that legacy sites offered almost double the percent of news (89 percent) in comparison with citizen news sites (56 percent) and three times that of blogs (27 percent)," said Margaret Duffy, faculty chair in strategic communication in the Journalism School. "The topic coverage on blogs and citizen new sites is generally narrow and the sourcing is light."

Duffy and Esther Thorson, associate dean for graduate studies at the school, along with Steve Lacy, professor at Michigan State University, and Dan Riffe, professor at the University of North Carolina, analyzed citizen news sites in 47 towns and cities across the United States. They found an average of fewer than two citizen news sites per city. Two-thirds of the sites were blogs, and the other sites contained news content.

"One of the biggest surprises we found was that mainstream media Web sites were almost as welcoming to citizen participation as citizen journalism sites, and they were far more welcoming than blogs," Thorson said. "Many industry professionals hope that citizen sites will democratize news media, but that hope has yet to be realized."

Results from second phase of the two-part study revealed that many of the citizen sites and blogs examined in the first phase had become dormant or disappeared. While some citizen sites and bloggers are doing well, many are struggling to survive and support their efforts, Duffy said.

Other key findings from the report include:

* Blogs were less likely than citizen news sites to permit posting comments or emailing the site.
* The majority of mainstream sites provided rules and policies for contributing stories and photos.
* Blogs and news sites were more likely than legacy media to post links within stories to outside sources.

However, citizen sites linked to legacy news sites twice as often as legacy sites linked to citizen sites. Citizen sites used legacy sites as news sources.

The study, "Tracking and Analyzing Community News Models," was funded by the Pew Charitable Trusts and the Knight Foundation. It recently was published in the State of the Media 2009 report by the Project for Excellence in Journalism. The study can be viewed by visiting: http://www.stateofthenewsmedia.org/ **-30-**

Parkinson's disease medication triggers destructive behaviors

Mayo Clinic study identifies at-risk patients

VIDEO ALERT: *Additional audio and video resources including excerpts from an interview with Dr. J. Michael Bostwick describing the research, are available on the Mayo Clinic News Blog.*

ROCHESTER, Minn. - A new study conducted at Mayo Clinic reports that one in six patients receiving therapeutic doses of certain drugs for Parkinson's disease develops new-onset, potentially destructive behaviors, notably compulsive gambling or hypersexuality.

The study extends findings from two Mayo case series published in 2005 that reported a connection between dopamine agonist medications and compulsive gambling or hypersexuality.

Dopamine agonists are a class of drugs that include pramipexole and ropinirole. They are commonly used to treat Parkinson's disease, but low doses also are used for restless legs syndrome. They uniquely stimulate brain limbic circuits, which are thought to be fundamental substrates for emotional, reward and hedonistic behaviors.

"The 2005 case series alerted us that something bad was happening to some unfortunate people. This study was done to assess the likelihood that this effect would happen to the average Parkinson's patient treated with these agents," says J. Michael Bostwick, M.D., Mayo Clinic psychiatrist who spearheaded the new study. It is published in the April issue of Mayo Clinic Proceedings.

The researchers analyzed the medical records of patients with Parkinson's disease residing in counties surrounding Rochester, Minn., who received their primary neurological care at Mayo Clinic in Rochester between 2004 and 2006. This group included 267 patients. Of those, 66 were taking dopamine agonists for their Parkinson's disease. Of those 66, 38 were taking the drugs in therapeutic doses (doses expected to be at least minimally beneficial).

The findings were definitive. Seven patients experiencing new-onset compulsive gambling or hypersexuality were taking dopamine agonists in therapeutic doses. None of the other Parkinson's disease patients developed compulsive gambling habits or hypersexuality, including the 28 patients on subtherapeutic dopamine agonist doses or the other 201 patients not taking dopamine agonists. None of the 178 patients treated only with the standard drug for Parkinson's disease, carbidopa/levodopa, developed these behaviors.

"It is crucial for clinicians prescribing dopamine agonists to apprise patients as well as their spouses or partners about this potential side effect. The onset can be insidious and overlooked until life-altering problems develop," says J. Eric Ahlskog, M.D., Ph.D., Mayo Clinic neurologist who co-authored and treated many of the patients in the 2005 study. "It also is worth noting that the affected patients were all taking therapeutic doses. Very low doses, such as those used to treat restless legs syndrome, carry much less risk."

"For some patients, a reduction in the dose of the dopamine agonist may prove to be sufficient treatment," says Dr. Ahlskog, "although total elimination of the offending drug is often necessary."

Wristbands ease nausea with cancer treatment

Cancer patients who wore acupressure wristbands had much less nausea while receiving radiation treatment, making the bands a safe, low-cost addition to anti-nausea medication, according to a study published in the Journal of Pain and Symptom Management by University of Rochester Medical Center researchers.
Previous research has suggested that the placebo effect – essentially, an outcome related to your body that you expect to happen - might be why elastic wristbands reduce nausea. However, the findings of the latest study do not support that notion, even though researchers continue to believe in the mind's powerful influence over symptoms.

"We know the placebo effect exists, the problem is that we don't know how to measure it very well," said Joseph A. Roscoe, Ph.D., corresponding author and research associate professor at the James P. Wilmot Cancer Center at URMC. "In this study we attempted to manipulate the information we gave to patients, to see if their expectations about nausea could be changed. As it turned out, our information to change people's expectations had no effect – but we still found that the wristbands reduce nausea symptoms."

The clinical trial enrolled 88 people divided into three groups. All had reported some degree of nausea after receiving at least two radiation treatments for any type of cancer. Although chemotherapy is more closely linked with producing nausea and vomiting, radiation to the intestinal tract can also cause nausea, Roscoe said.

Patients without wristbands, or group 1, served as the control group. The patients who wore wristbands were divided into two groups. Group 2 received an informational handout explaining that in previous research, wristbands were found to reduce nausea. The handout also showed two bar graphs reflecting a reduction in nausea among people who wear the bands. Group 3 also received a handout, but the information was more neutral.

The result: a 23.8 percent decrease in nausea for all the patients who wore wristbands, compared to a 4.8 percent decrease in the control group. But when researchers analyzed whether any differences existed between the two wristband groups, none was found.

"Some of our body's feelings and sensations are ambiguous and subject to interpretation," Roscoe explained. "Your mind cannot make a blister go away, or reduce hair loss, but it can interpret ambiguous abdominal sensations and decide how much nausea they represent, based on our expectations."

Roscoe has conducted several previous studies of how expectations influence treatment side effects, and how wristbands can ease chemotherapy-related nausea. The American Cancer Society funded the current study.

Targeting the wrist as a nausea point is a staple of Chinese acupuncture medicine. Stimulating that point on the wrist with a needle or the pressure of an elastic band is said to unblock the flow of universal chi energy.

Scientists identify key gene that protects against leukemia

Researchers have identified a gene that controls the rapid production and differentiation of the stem cells that produce all blood cell types - a discovery that could eventually open the door to more streamlined treatments for leukemia and other blood cancers, in which blood cells proliferate out of control.

Additionally, in investigating the mechanisms of this gene, the scientists uncovered evidence that could lead to a protocol for bone marrow transplants that could boost the chance of a cure in some patients.

The research, led by Emmanuelle Passegué, PhD, of the University of California, San Francisco, demonstrates that the JunB gene is at the center of a complex network of molecular and environmental signals that regulate the proliferation and differentiation of hematopoietic stem cells, the multipotent, self-renewing cells that give rise to all blood cell types.

In the study published April 7, 2009, in the journal Cancer Cell, Passegué's team studied the behavior of JunB-deficient HSCs in both the culture dish and when transplanted into mice. In every case in which engraftment of the HSCs occurred in the mice, the scientists noted a progressive expansion of the myeloid lineage, which constitutes a type of mature white blood cell that fights infection. This expansion led by 6 to 12 months post-transplantation to the development of a myeloproliferative disease, which can evolve to leukemia. The finding indicated that the proliferating JunB-deficient HSCs causes leukemia.

Like traffic lights, which limit speed, direct the flow of vehicles and prevent accidents, JunB curtails both the rate at which HSCs are proliferating and the rate of differentiation toward the myeloid lineage that ultimately results in leukemia. The striking analogy inspired the image for the cover of Cancer Cell's April 7 issue.

Without JunB, HSCs lose their ability to respond to signals from the protein receptors Notch and TGF-beta, which reside on the cells' surface and play critical roles in determining cell fate.

"By uncovering this mechanism, we might one day be able to determine the difference between normal HSCs and leukemic stem cells in gene regulatory networks. This could allow us to develop more targeted therapies. These kinds of therapeutic applications are still down the road, but they can happen very quickly in the blood/leukemia field," says Passegué.

Passegué's study represents a turnabout from other research, which has demonstrated that mutated HSC that cause leukemia burn out at a faster rate than normal HSCs. In contrast, this study shows that JunB does not effect the cells' potential for unlimited self-renewal.

The researchers demonstrated this by treating both JunB-deficient mice and control mice with the powerful chemotherapy drug 5-FU, which was given to deplete regenerating HSCs. As expected, JunB-deficient mice consistently displayed higher levels of myeloid lineage than the control group, indicating constant regeneration of a myeloproliferative disease from JunB-deficient HSCs that persisted after treatment. When researchers compared survival rates of the animals during several cycles of treatment, they found little difference between the two groups, indicating that JunB-deficient HSCs do not exhaust faster than the control HSCs.

In tracking the differences between the JunB-deficient mice and the control group, it became apparent to the researchers that purity of HSCs was a key factor in determining the success of engraftment. Initially, the scientists were struck by the disparity in engraftment between the JunB-deficient HSCs and the control HSCs. But with the use of SLAM cells, a highly purified HSC population, they found that the two groups displayed in fact identical engraftment.

This finding may have important ramifications for patients undergoing bone marrow transplants, for leukemia, lymphoma, multiple myeloma and certain cancers.

"Currently, patients undergoing bone marrow transplants may not be getting enough of the quiescent transplanted HSCs that are optimal for successful engraftment," says Passegué. Using a highly purified HSC population could be more beneficial."

Senior author Passegué and first author Marianne Santaguida, PhD, are from the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF. Co-authors from the same center are Koen Schepers, PhD, and

Bryan King. Other co-authors are Benjamin Braun, MD, PhD, and Amit Sabnis, MD, of the UCSF Department of Pediatrics; E. Camilla Forsberg, PhD, of the Institute for Biology of Stem Cells at University of California, Santa Cruz, and Joanne Attema, PhD, of the Institute for Experimental Medical Science at Lund University, Sweden. Research was funded by grants from the Concern Foundation, UCSF Research Evaluation and Allocation Committee and the NIH.

Drug shows activity in men with advanced prostate cancer

A new multi-center study shows that an experimental drug lowers prostate specific antigen (PSA) levels – a marker for tumor growth – in men with advanced prostate cancer for whom traditional treatment options have failed. The study, led by researchers at Memorial Sloan-Kettering Cancer Center (MSKCC), is published today in Science Express, the online version of the journal Science.

Most men with metastatic prostate cancer eventually build up resistance to the drugs that lower or block male hormones and develop a more aggressive form of the illness called castration-resistant prostate cancer (CRPC), or hormone-refractory disease. According to the study's findings, investigators studied two novel compounds, RD162 and MDV3100, and not only gained an understanding of their novel mechanism of action, but found that these agents showed activity in CRPC cells in culture and in mice.

The study also reports on a Phase 1/2 trial of MDV3100 in 30 patients with advanced CRPC and found that 22 out of 30 men showed declining PSA levels, and 13 out of 30 men (43 percent) had PSA levels fall by more than half.

Several years ago, the senior author of the study, Charles Sawyers, MD, and his colleagues at the University of California, Los Angeles (UCLA), uncovered a potential reason why metastatic prostate cancer patients eventually relapse with CRPC. This insight was used to discover RD162 and MDV3100.

"It's gratifying to know that our hypotheses about why men develop resistance to currently available treatments are confirmed and, most importantly, that there are already patients who are benefiting from our research," said Dr. Sawyers, Chair of the Human Oncology and Pathogenesis Program at MSKCC and a Howard Hughes Medical Institute investigator.

Current treatments for men who have advanced prostate cancers inhibit the activity of male hormones that help drive tumor growth. Many of these drugs disrupt the androgen (male hormone) receptor, which helps regulate cell proliferation, but tumors eventually become resistant to the drugs by expressing higher levels of the receptor. Preclinical studies by Dr. Sawyers and others have demonstrated that CRPC cells have increased expression of the androgen receptor and that overexpression of this receptor may contribute to the progression of disease.

Based on this information, Dr. Sawyers initiated a collaboration with Michael Jung, PhD, Professor of Chemistry at UCLA, that led to the discovery of a number of nonsteroidal, small molecule antiandrogen compounds, including MDV3100, which has been shown to retain its anticancer activity, even when the receptor's expression is elevated.

"The discovery and initial development of this drug was a collaborative effort all done in the academic setting, without reliance on the engine of the pharmaceutical industry that typically drives drug development," said Dr. Sawyers. Dr. Jung's group synthesized the compounds, which Dr. Sawyers' team then evaluated using prostate cancer mouse models engineered to highly express the androgen receptor, mimic progression to castration-resistant disease, and reflect the biology of clinical drug resistance.

According to the new study, the team of researchers tested various compounds to block the androgen receptor in CRPC cells. They chose to further evaluate the drug RD162 and a closely related compound, MDV3100. According to their findings, both drugs inhibit the androgen receptor function by impairing the receptor's ability to enter a CRPC cell's nucleus (called nuclear translocation), blocking it from binding to the DNA of its target genes, and preventing the cell from growing. They found that both compounds worked well in cells in culture, shrank tumors in mice, maintained tumor shrinkage for months, and prevented the androgen receptor from activating additional genes later in the process, or "downstream." Other currently approved drugs cannot disable the receptor in such a way.

The biopharmaceutical company Medivation, Inc., licensed RD162 and MDV3100 from UCLA in 2006 and has already completed enrollment in the first human trial of oral MDV3100 - a Phase 1/2 clinical trial, which was led by investigators at MSKCC and conducted through the Prostate Cancer Clinical Trials Consortium. The Consortium is sponsored by the Department of Defense and the Prostate Cancer Foundation. The trial enrolled men with metastatic, castration-resistant prostate cancer who relapsed after treatment with conventional hormone therapy and demonstrated anti-prostate cancer effects beginning with the first patient treated with MDV3100 at the lowest dose. Further positive results from an additional 110 patients who received the drug at higher doses were recently reported at the ASCO Genitourinary Cancers Symposium in February 2009 ***(see abstract).***

"The declines in PSA levels observed thus far and the general tolerability of this treatment are encouraging," said Howard Scher, MD, a study co-author and Chief of the Genitourinary Oncology Service at MSKCC. "I am looking forward to continuing the study of this drug, which has the potential to be a powerful tool in a limited arsenal of treatments against this deadly form of the disease." A Phase 3 trial is planned to begin later this year.
Researchers at MSKCC, UCLA, Oregon Health and Science University, University of Washington, Seattle, and Medivation, Inc., contributed to the research. Dr. Sawyers and several of the study's authors are co-inventors on patent applications covering RD162, MDV3100, and related compounds.
The study was supported in part by the Prostate Cancer Foundation, the National Cancer Institute, and a Prostate Cancer Research Program Clinical Consortium Award.

Vitamin D may exacerbate autoimmune disease

Deficiency in vitamin D has been widely regarded as contributing to autoimmune disease, but a review appearing in Autoimmunity Reviews explains that low levels of vitamin D in patients with autoimmune disease may be a result rather than a cause of disease and that supplementing with vitamin D may actually exacerbate autoimmune disease.

Authored by a team of researchers at the California-based non-profit Autoimmunity Research Foundation, the paper goes on to point out that molecular biologists have long known that the form of vitamin D derived from food and supplements, 25-hydroxyvitamin D (25-D), is a secosteroid rather than a vitamin. Like corticosteroid medications, vitamin D may provide short-term relief by lowering inflammation but may exacerbate disease symptoms over the long-term.

The insights are based on molecular research showing that 25-D inactivates rather than activates its native receptor - the Vitamin D nuclear receptor or VDR. Once associated solely with calcium metabolism, the VDR is now known to transcribe at least 913 genes and largely control the innate immune response by expressing the bulk of the body's antimicrobial peptides, natural antimicrobials that target bacteria.

Written under the guidance of professor Trevor Marshall of Murdoch University, Western Australia, the paper contends that 25-D's actions must be considered in light of recent research on the Human Microbiome. Such research shows that bacteria are far more pervasive than previously thought – 90% of cells in the body are estimated to be non-human – increasing the likelihood that autoimmune diseases are caused by persistent pathogens, many of which have yet to be named or have their DNA characterized.

Marshall and team explain that by deactivating the VDR and subsequently the immune response, 25-D lowers the inflammation caused by many of these bacteria but allows them to spread more easily in the long-run. They outline how long-term harm caused by high levels of 25-D has been missed because the bacteria implicated in autoimmune disease grow very slowly. For example, a higher incidence in brain lesions, allergies, and atopy in response to vitamin D supplementation have been noted only after decades of supplementation with the secosteroid.

Furthermore, low levels of 25-D are frequently noted in patients with autoimmune disease, leading to a current consensus that a deficiency of the secosteroid may contribute to the autoimmune disease process. However, Marshall and team explain that these low levels of 25-D are a result, rather than a cause, of the disease process. Indeed, Marshall's research shows that in autoimmune disease, 25-D levels are naturally down-regulated in response to VDR dysregulation by chronic pathogens. Under such circumstances, supplementation with extra vitamin D is not only counterproductive but harmful, as it slows the ability of the immune system to deal with such bacteria.

The team points out the importance of examining alternate models of vitamin D metabolism. "Vitamin D is currently being recommended at historically unprecedented doses," states Amy Proal, one of the paper's co-authors. "Yet at the same time, the rate of nearly every autoimmune disease continues to escalate."
For the past five years, Autoimmunity Research Foundation has been running an observational study in which patients are administered pulsed low dose antibiotics and a VDR agonist in order to kill chronic bacteria implicated in their diseases. Specific data on the cohort was recently presented by CAPT Thomas H. Perez, USPHS (ret) at the International Congress on Autoimmunity in Porto, Portugal:
***Transcript**: http://autoimmunityresearch.org/transcripts/ICA2008_Transcript_TomPerez.pdf*
***Video**: http://vimeo.com/1789735*

Doctors tune in to the source of back pain

TUNING forks, brushes and erasers can all help to quickly and cheaply reveal which painkiller to prescribe for back pain.

From a patient's description, doctors struggle to distinguish between neuropathic pain from nerve damage, such as in sciatica, and pain from inflammation, yet each requires a different painkiller. Only expensive tests such as MRI scans reveal the source precisely, leading Joachim Scholz of Massachusetts General Hospital in Boston and his colleagues to look for a quicker, cheaper way.

The team compiled a list of quick questions and physical tests and assessed the response of patients diagnosed with each type of pain. From this, they whittled the list down to **six questions** and 10 physical tests that included rubbing brushes, safety pins, tuning forks and pencil erasers on the back. Together, the tests can show whether or not the pain is neuropathic (PLoS Medicine, DOI: 10.1371/journal.pmed.1000047).
The whole list takes just 15 minutes to complete and also distinguishes between three types of neuropathic pain.

Ancestors of African Pygmies and neighboring farmers separated around 60,000 years ago

All African Pygmies, inhabiting a large territory extending west-to-east along Central Africa, descend from a unique population who lived around 20,000 years ago, according to an international study led by researchers at the Institut Pasteur in Paris. The research, published April 10 in the open-access journal PLoS Genetics, concludes that the ancestors of present-day African Pygmies and farmers separated ~60,000 years ago.

Pygmies are characterized by a forest-dwelling hunter-gathering lifestyle and distinctive cultural practices and physical traits (e.g., low stature). Two groups of Pygmy populations live in the African rainforests: the "Western Pygmies" and the "Eastern Pygmies". The common origins of the two groups of Pygmies, separated by thousands of kilometers, have been long debated, and their relationships with neighboring farmers remained obscure.
The researchers, led by Lluis Quintana-Murci, studied the genetic profile of twelve populations of Pygmies and neighboring farmers dispersed over the African continent, using sequence data from non-coding regions of their genomes. Using simulation-based procedures, they determined that the ancestors of Pygmy hunter-gatherers and farming populations started to diverge ~60,000 years ago, coinciding with a period of important human migration both within and outside Africa. Much later, ~20,000 years ago, Western and Eastern Pygmies separated, concurrently with a period of climate change leading to large retreats of the equatorial rainforest into refugia.

The common origin of all Pygmies unmasked in this study led Etienne Patin, one of the leading authors, to conclude that "they have probably inherited their distinctive shared physical traits, such as low height, from a common ancestor, rather than by convergent adaptation to the rainforest". However, complete genome-wide profiles of these populations are now needed, both to characterize more precisely their demographic history and to identify genes involved in the adaptation of these populations with different lifestyles to their specific ecological habitats.

CITATION**: Patin E, Laval G, Barreiro LB, Salas A, Semino O, et al. (2009) Inferring the Demographic History of African Farmers and Pygmy Hunter-Gatherers Using a Multilocus Resequencing Data Set. PLoS Genet 5(4): e1000448. doi:10.1371/journal.pgen.1000448* ***http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1000448

Tax lobbying provides 22,000 percent return to multinational firms, KU researchers find

A recent tax law change provided a tax break to the corporations by lowering their tax rate 85 percent on certain worldwide income

LAWRENCE, Kansas - Three professors at the University of Kansas have found that a one-time tax break allowed multinational corporations to receive a 22,000 percent average return on lobbying expenditures.

The study was conducted by Raquel Meyer Alexander, assistant professor of accounting; Stephen Mazza, associate dean of the School of Law; and Susan Scholz, associate professor of accounting and Harper Faculty Fellow. Mazza recently presented their findings at the Critical Tax Theory Conference, sponsored by the Indiana University Maurer School of Law in Bloomington.

A recent tax law change provided a tax break to the corporations by lowering their tax rate 85 percent on certain worldwide income. The professors examined the extensive lobbying around the law change and found that for each dollar spent on lobbying, a corporation received $220 in U.S. income tax savings.
The American Jobs Creation Act, among other provisions, allowed U.S. multinational corporations a one-time opportunity to bring home foreign earnings at an extremely low tax rate. In effect, it lowered the corporate income tax rate from 35 percent to a maximum of 5.25 percent on repatriated amounts. In response, 843 firms repatriated over $312 billion at this reduced tax rate. Using financial disclosures in the annual reports of multinational corporations, the researchers examined 476 publicly traded firms that repatriated more than $298 billion.

More than 105 companies repatriated more than $500 million. The firms with the largest repatriation amounts include Pfizer, Merck & Co., Hewlett Packard, Johnson & Johnson and IBM. Pfizer repatriated $37 billion, which represented nearly 30 percent of its total assets and 70 percent of its revenue in 2004. In the financial industry, Citigroup, JP Morgan, Morgan Stanley, Merrill Lynch and General Electric repatriated a total of $12.1 billion. Using empirical techniques to study the characteristics of these firms, Alexander, Mazza

and Scholz conclude that repatriation provided significant tax savings to a relatively small group of larger, older and more profitable companies.

Further, the KU professors found that firms lobbying for the repatriation provision received lucrative returns on their lobbying investment. On average, firms generated a 22,000 percent return on tax lobbying. When the researchers examined the firms investing more than $1 million in tax lobbying, the return jumped to 24,300 percent. For example, Eli Lilly & Co. disclosed spending $8.52 million in 2003 and 2004 lobbying for this provision. In return, the company gained a tax savings of more than $2 billion.

Alexander, Mazza and Scholz conclude that the tax policy implications are troubling. Many economic development policies are aimed at supporting emerging firms and industries. This tax provision appears to be doing the opposite as it provides tax subsidies to well-established and highly profitable firms and industries.

Mazza hopes this study informs elected officials when similar provisions are introduced."Perhaps it is time for a national conversation about the role of lobbyists in tax reform. We should be concerned when a corporation's most lucrative investment is in lobbying the government for tax benefits."

More women with early stage breast cancer choosing double mastectomies

A University of Minnesota cancer surgeon and researcher has found a dramatic increase in the number of women diagnosed with the earliest stage of breast cancer choosing to have both breasts surgically removed.

The rate of contralateral prophylactic mastectomy (CPM) surgery among U.S. women with ductal carcinoma in situ (DCIS) increased by 188 percent between 1998 and 2005, according to Todd Tuttle, M.D., lead researcher on this study.

Tuttle is associate professor of oncologic surgery with the University of Minnesota Medical School and a researcher with the University's Masonic Cancer Center. The National Cancer Institute sponsored this research study and the findings are published in the current issue of the Journal of Clinical Oncology.

"The 10-year survival rate for women with DCIS is 98 to 99 percent," Tuttle said. "Therefore, removal of the normal contralateral breast will not improve the excellent survival rates for this group of women. Nevertheless, many women, particularly young women, are choosing to have both breasts removed."

In a previous research study, Tuttle and his colleagues found more American women choosing to have both breasts removed when cancer has been found in only one breast.

This new study indicates the same attitude among women with DCIS, described as the earliest stage of breast cancer when the cancer is small and confined within a duct area of the breast. At this stage, the disease is considered highly treatable with breast-conserving surgery and radiation or hormone therapy. However, if the cancer is aggressive in nature or the woman is not in treatment, DCIS can progress either into invasive, more serious cancer in the affected breast, or it can develop in the other healthy breast.

Tuttle and his colleagues used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to evaluate information about 51,030 women diagnosed with DCIS in one breast between 1988 and 2005. They found that 2,072 (13.5 percent) of the women chose breast removal surgery for their DCIS treatment. Furthermore, between 1998 and 2005 the rate of women opting for the surgery increased by 188 percent.

Breast cancer affects more than 214,000 women in the U.S. each year; more than 3,000 of those women are Minnesotans.

Researchers working with Tuttle on this study were S. Jarosek, EB Habermann, A Arrington, TJ Morris, and BA Virnig, all with the University of Minnesota in Minneapolis.

Do aliens share our genetic code?

* 14:02 09 April 2009 **by Lewis Dartnell**

What similarities will alien life forms have to living things here on Earth? We won't know until we find some, but now there is evidence that at least the basic building blocks will be the same.

All terrestrial life forms share the same 20 amino acids. Biochemists have managed to synthesise 10 of them in experiments that simulate lifeless prebiotic environments, using proxies for lightning, ionising radiation from space, or hydrothermal vents to provide the necessary energy. Amino acids are also found inside meteorites formed before Earth was born.

Paul Higgs and Ralph Pudritz at McMaster University in Hamilton, Ontario, Canada, point out that all these experiments produced a subset of the same 10 amino acids and calculate that these 10 require the least amount of energy to form.

This, they argue, suggests that if alien life exists it probably has the same 10 amino acids at its core.

Universal code?

They show how the other 10 may have been added one by one as early life on Earth became more sophisticated. More controversially, they go on to argue that this process dictated the evolution of the genetic code, suggesting it too is universal.

Darren Griffin, a geneticist at the University of Kent, UK, suggests Higgs and Pudritz are pushing their conclusions too far.

"Laws of physics govern the universe, and it seems reasonable to suggest that there are laws of molecular biology that may also be universal," he says. "But it seems unlikely that the very same genetic code would arise on another planet, even if there are similarities in the fundamental molecules such as amino acids."

Scientists pinpoint the 'edge of space'

Canadian technology on NASA mission is a prototype for future, longer mission

Where does space begin? Scientists at the University of Calgary have created a new instrument that is able to track the transition between the relatively gentle winds of Earth's atmosphere and the more violent flows of charged particles in space – flows that can reach speeds well over 1000 km/hr. And they have accomplished this in unprecedented detail.

Data received from the U of C-designed instrument sent to space on a NASA launch from Alaska about two years ago was able to help pinpoint the so-called edge of space: the boundary between the Earth's atmosphere and outer space. With that data, U of C scientists confirmed that space begins 118 km above Earth and the results were published this week in the Journal of Geophysical Research.

The instrument – called the Supra-Thermal Ion Imager – was carried by the JOULE-II rocket on Jan. 19, 2007. It travelled to an altitude of about 200 kilometers above sea level and collected data for the five minutes it was moving through the "edge of space." The Canadian Space Agency invested $422,000 in the development of the Supra-Thermal Ion Imager instrument on JOULE-II.

The ability to gather data in that area is significant because it's very difficult to make measurements in this region, which is too high for balloons and too low for satellites.

"It's only the second time that direct measurements of charged particle flows have been made in this region, and the first time all the ingredients – such as the upper atmospheric winds – have been included," says David Knudsen, associate professor in the Department of Physics and Astronomy at the University of Calgary.

Knudsen and his former PhD student Laureline Sangalli are the lead authors of the paper. Co-authors include: JOULE-II lead scientist Miguel Larsen of Clemson University, Robert Pfaff and Douglas Rowland of NASA Goddard Space Flight Center and T. Zhan of Conseco Inc.

"When you drag a heavy object over a surface, the interface becomes hot. In JOULE-II we were able to measure directly two regions being dragged past each other, one being the ionosphere - being driven by flows in space - and the other the earth's atmosphere," says Knudsen, who also is the head of the Space Physics Division of the Institute for Space Imaging Sciences (ISIS). The institute is a research partnership between the University of Calgary and University of Lethbridge.

The measurements confirmed what other scientists consider the boundary or edge of space.

"The results have given us a closer look at space, which is a benefit to pure research in space science," Knudsen says. "But it also allows us to calculate energy flows into the Earth's atmosphere that ultimately may be able to help us understand the interaction between space and our environment. That could mean a greater understanding of the link between sunspots and the warming and cooling of the Earth's climate as well as how space weather impacts satellites, communications, navigation, and power systems."

The U of C-designed instrument has been adopted by COM DEV, an Ontario-based global designer and manufacturer of space hardware, and is being used as a prototype for three instruments currently being readied to fly on the European Space Agency's "Swarm" satellite mission, set to launch late next year and to collect data for four years. The JOULE-II instrument is one in a long list of more than a dozen instruments designed by U of C scientists in the past forty years which have flown in space. There are at least five more being readied to go on missions in the next two years.

"Understanding the boundary between the Earth's atmosphere and outer space is fundamental to the bigger picture of the effects of space on the Earth's climate and environment," says Russ Taylor, the director of ISIS and head of the Department of Physics and Astronomy at the U of C. "This detection is part of a long history of success by ISIS researchers in designing and building innovative instruments flown on rockets and satellites to image the flow of matter and energy between the Earth and Space."

The paper "Rocket-based measurements of ion velocity, neutral wind, and electric field in the collisional transition region of the auroral ionosphere" was published this week in the Journal of Geophysical Research. It can be found on-line at http://www.agu.org/journals/ja/

Device Protects Transplanted Pancreatic Cells from the Immune System

LA JOLLA, Calif.- Scientists at Burnham Institute for Medical Research (Burnham) and the University of California San Diego (UC San Diego) School of Medicine have demonstrated in mice that transplanted pancreatic precursor cells are protected from the immune system when encapsulated in polytetrafluorethylene (PTFE). The study, which suggests a new approach to treating Type 1 diabetes, was published online on April 8 in the journal Transplantation.

The team of scientists showed that after transplantation, the precursor cells mature into functional beta cells that are glucose-responsive and control blood sugar levels. Additionally, the study demonstrated that using precursor cells, instead of more committed beta cells, enhanced the cell transplant's chances of success.

"The results exceeded our expectations," said Pamela Itkin-Ansari, Ph.D., assistant adjunct professor at the UC San Diego School of Medicine and Burnham. "We thought that T-cells, although unable to penetrate the device, would cluster around it. But we found no evidence of an active immune response, suggesting that the cells in the device were invisible to the immune system."

The investigators used two different mouse models in the study. The team transplanted mouse islet cells into other mice to demonstrate that the cells were protected from the immune system when encapsulated in PTFE. Human cells encased in PTFE were then transplanted into immunodeficient mice to study the viability and function of both mature beta cells and precursor cells inside the device. Itkin-Ansari's team found that by using precursor cells that had not completely differentiated, the transplanted cells could regenerate into fully functional beta cells. This has important implications for how stem cell-derived tissue should be transplanted in the future.

Type 1 diabetes results from an autoimmune response wherein the body attacks and kills insulin producing beta cells in the pancreas. One of the challenges of cell transplantation therapy to treat diabetes is the need for long term immunosuppression, which carries health risks. Transplanting beta cells in a protective device could alleviate the need to use immunosuppressive drugs.

This study was funded by grants from the Juvenile Diabetes Research Foundation, the National Institute of Diabetes and Digestive and Kidney Diseases and the JW Kieckhefer Foundation.

DNA analysis may be done on Mars for first time

* 17:03 09 April 2009 **by Ewen Callaway**, Boston

In August 1996, molecular biologist Gary Ruvkun was about to reveal one of the biggest discoveries of his scientific career. His lab at Harvard Medical School had recently found a gene called age-1 that determines lifespan in roundworms. Their work offered the tantalising possibility that tinkering with molecular pathways might extend the lifespan of other organisms – and perhaps even humans.

Harvard sent out a press release and Ruvkun prepared for an onslaught of media attention. But it never came. Two days before his team's paper came out, scientists analysing a meteorite from Mars called ALH84001 made headlines worldwide. Then-US president Bill Clinton even got in on the announcement.

"My grad student leans in the door and says, 'They've just announced life on Mars,'" recalls Ruvkun. "That would really f - us," Ruvkun replied, thinking his student was joking.

Scientists have since raised serious doubts about the existence of the purported fossilised microbes in the meteorite (see image).

But now, more than a decade after his work was overshadowed by news of possible life on Mars, Ruvkun has joined the hunt to find it. Moreover, he and his colleagues want to sequence its DNA.

Toehold for life

Today, Mars is a frozen, barren world. Ultraviolet light and energetic space particles stream in through its thin atmosphere, sterilising any life – at least as we know it – on its bone-dry surface. But recent research suggests life might find a niche just below the surface, where liquid water could be widespread. The discovery of plumes of methane in the planet's atmosphere also hints at subsurface life, since some terrestrial microbes produce the gas.

Chemical signs of life can be ambiguous, but Ruvkun and his team hope to find its unequivocal signature by sending a DNA amplifier and sequencer to Mars in the next decade. They're betting that any life on the Red Planet shares an evolutionary heritage with life on Earth, and therefore contains a similar genetic code – a requirement that other scientists say is too narrowly focused, since Martian life may have evolved independently and therefore may have very different chemistry.

"This is a pure jackpot scheme. You either discover the most important thing for a long time, or you discover nothing," says Ruvkun, who in 2008 won the Lasker Award, an honour shared by 75 scientists who later went on to nab a Nobel.

Interplanetary travel

Why would Martian life be similar to that on Earth? About 4 billion years ago, when terrestrial life probably got its start, rocky bodies were flying through the solar system and slamming into the planets. These impacts threw pieces of the planets into space, and some of these pieces landed on other planets as meteorites.

Ancient microbes might have hitched a ride to or from Mars on these meteorites. While in space, the surfaces of these rocks would have been sterilised by UV radiation and then singed to a crisp entering the atmosphere. But a large enough rock could support life beneath its surface, Ruvkun says.

And life originating or landing on Mars some 4 billion years ago may well have found the environment there hospitable. The planet may have boasted a thicker atmosphere and liquid water on its surface, possibly in the form of oceans.

"Mars was probably fit for life," says Paul Davies, a cosmologist and astrobiologist at Arizona State University in Tempe, who is not involved in the sequencing project.

Early prototype

NASA has bought into the possibility that life may have once travelled between the two planets and is supporting early development of the sequencing project, called the Search for Extraterrestrial Genomes (SETG).

The agency has already provided just under $2 million in funding for the project, says Christopher Carr, an engineer in Ruvkun's lab who is spearheading development of the device.

The latest prototype rests on a metal breadboard at one end of Carr's lab bench, connected to a series of hydraulic pumps, electric wires and cables. A more svelte, compact version of the instrument may one day travel to Mars, perhaps on a mission planned for launch in 2018.

DNA glow

How would such an instrument work? Carr divides the project into four distinct stages.

The first is preparing a sample from soil or ice that a future Mars lander gathers from burrowing into the planet's surface.

After this sample is reconstituted in liquid and mixed with a dye that fluoresces when it binds onto DNA, the device will funnel the sample through a glass microfluidic chip filled with hundreds of tiny channels. If one channel glows positive for DNA, its contents will move on to the next stage – amplification.

It's no understatement to say that polymerase chain reaction (PCR) revolutionised the practice of biology when it was invented in the 1980s. The technology allows researchers to create billions of identical copies of a short stretch of DNA, simply by knowing the genetic sequence of its two ends.

It's also astonishingly sensitive and simple, requiring little more than a single 'template' DNA molecule, a heat source and some raw chemical materials. "PCR is done in junior high school," Ruvkun told New Scientist. "That's the definition of what you want to send to Mars."

Sequencing technologies

To determine whether DNA on Mars shares ancestry with terrestrial life, his team will amplify a gene called the 16S ribosomal RNA subunit. It encodes an RNA molecule that's part of the ribosome, a cell's crucial protein factory.

Ruvkun's team isn't yet sure how they'll decode the amplified DNA. The same sequencing technologies that might deliver a $1000 complete human genome sequence in the next few years could also read much shorter stretches of DNA on Mars. But simpler and slower gene-sequencing technologies might also do the job, Carr says.

If the experiment isolates, amplifies and sequences Martian DNA, the next step will be to determine how the sequence relates to Earth life and to rule out the possibility of terrestrial contamination, a major concern with PCR.

Contamination test

If Earth and Mars exchanged life 3-4 billion years ago, Mars life will stand out like an island species that has been isolated from the mainland. Ruvkun's team will make the call by comparing any 16S sequences they find on Mars with those known on Earth.

Because of its essential role in building cells' ribosomes, the gene has barely mutated over the past 4 billion or so years, allowing geneticists to gauge evolutionary relationships between distantly related organisms.

If the Martian DNA is distantly related to Earth life, its 16S sequence should plant it near the base of Earth's tree of life. On the other hand, a sequence that looks closely related to earthly organisms, such as E. coli or Salmonella bacteria, for instance, would be evidence for contamination.

Field tests

Team members are wrangling for a spot on a NASA Mars mission tentatively scheduled for liftoff in 2018. They plan to begin field-testing their device in Mars-like conditions on Earth, such as the Copahue Volcano in Argentina or Antarctica's dry valleys, in the next three years.

But the researchers admit they are a long way, not to mention tens of millions of dollars in funding, from launch. "Our goal is to make this instrument small enough that they can't say no to put it on a lander," Ruvkun says.

Others are taking SETG seriously, too. NASA has renewed the project's initial grant, and MIT planetary scientist Maria Zuber has taken a leading role in the team. "Maria is totally in the loop at NASA, and it lends [SETG] a level of credibility that could never come from us," Ruvkun says.

First things first

Norman Pace, a microbiologist at the University of Colorado in Boulder who studies life in extreme places on Earth, is more sceptical. He says sequencing DNA on Mars is "technologically feasible", but he thinks DNA searches should come after scientists discover other signatures for life on Mars.

"If you have DNA from Mars, it's worth sequencing," Pace says. "But having DNA from Mars is about as practical at this stage of the game as having DNA from that planet around Alpha Centauri."

Paul Davies worries that searching for DNA opens too narrow a window to the past. "If what you're hoping to do is look for traces of past life on Mars, then DNA isn't a very good biomarker – it's not going to survive for very long."

Indeed, SETG could only detect existing or recently extinct life on Mars. Carr puts the outer boundary under 1 million years, though it could be far less.

Generalist approach

Davies argues that searches for extraterrestrial life should instead focus on more general features of life. All amino acids that make up biological proteins, for instance, display a left-handed orientation, or chirality. "That, to me, is the most urgent thing," he told New Scientist. "You look for chirality, then mess around with DNA."

An instrument to search for signs of chirality, called Urey, may launch on Europe's ExoMars lander, which is now set to launch in 2016. Researchers will try to use its data to determine whether any chirality found is from life.

Would Urey be able to test, like SETG, whether any life on Mars has a common origin with that on Earth? Possibly, says instrument team leader Jeffrey Bada of the University of California, San Diego. "If the structural variety of amino acids was identical to that on Earth and they were also left-handed, we might well be related," Bada told New Scientist.

Definitive test

However, Ruvkun and his colleagues brush aside such concerns, saying that Martian DNA detection will go hand-in-hand with efforts to find more generic chemical signatures of life. They also contend that their experiment would provide a definitive test of the hypothesis that Earth and Mars exchanged life that still lives on Mars.

And then there's the simple "wow" factor of sending a DNA sequencer to another planet to search for life.

Michael Finney, a biotechnology entrepreneur on the team who conceived of SETG along with Ruvkun, says one engineer he approached saw an added bonus to joining their search for Martian genes.

"He had a reaction a lot of people had: 'I would love to work on this project because it would give me so much credibility with my eight-year-old,'" Finney says. "A lot of people on the whole project are letting their inner eight-year-olds speak."

Test quickly assesses whether Alzheimer's drugs are hitting their target

A test developed by physician-scientists at Washington University School of Medicine in St. Louis may help assess more quickly the ability of Alzheimer's drugs to affect one of the possible underlying causes of Alzheimer's disease in humans, accelerating the development of new treatments.

Scientists used the test to show that an Alzheimer's drug given to healthy volunteers reduced production of a substance known as amyloid beta (A-beta), a normal byproduct of human metabolism that builds to unhealthy levels forming brain plaques in Alzheimer's patients. The drug candidate, LY450139, which is also known as semagacestat, is being studied in clinical trials by Eli Lilly and Company.

Ongoing clinical trials are studying the effect that semagacestat may have on cognitive function and biochemical and brain imaging biomarkers in patients with Alzheimer's disease. Washington University researchers wanted to see whether the new measurement technique, stable isotope-linked kinetics (SILK), could detect the study drug's impact on A-beta synthesis in healthy volunteers.

"Bringing an Alzheimer's disease drug into clinical trials from tests in animal models has always been challenging," says study director Randall Bateman, M.D., a Washington University neurologist who treats

patients at Barnes-Jewish Hospital. "We haven't had a way to quickly and accurately assess a drug's effects, and that meant there always had to be some degree of educated guesswork when it came to setting the optimal dosage for humans. SILK may help to eliminate much of that guesswork."

The results appear online in Annals of Neurology on April 10.

Scientists are unsure whether increased A-beta production, reduced clearance or a combination of the two lead to the A-beta buildup in the brain, a process that many believe triggers Alzheimer's disease. Bateman and his colleagues are currently using SILK to try to answer this question.

Until SILK, there has not been a way to directly measure the production or clearance of A-beta. The efficacy of potential new Alzheimer's drug candidates has been assessed by monitoring the cognitive functions of patients with the disease for extended periods of time, which require large, lengthy and expensive studies.

In their double-blind study, scientists gave 20 healthy volunteers varying doses of either a study drug or a placebo. At the start of the SILK test, volunteers were connected to an intravenous drip that gave them a slightly altered form of the amino acid leucine, which is a component of A-beta.

Over the course of several hours, cells in the brain picked up the labeled leucine and incorporated it into the new copies made of A-beta and other proteins. The scientists took periodic samples of the subjects' cerebrospinal fluid to determine how much of the A-beta included altered leucine.

Tracking the rise of the percentage of labeled A-beta over time reveals the A-beta production rate. Scientists then stop the leucine labeling but continue analyzing spinal fluid samples. As the body removed old A-beta and made new A-beta, the percentage of A-beta containing altered leucine dropped, revealing the A-beta clearance rate. The results suggest a dose-dependent drop in A-beta production, with an 84 percent reduction in A-beta production being measured with the highest study drug dose.

The SILK procedure takes 36 hours, but provides scientists a more detailed assessment of amyloid beta production and clearance levels than they can obtain through conventional methods.

"You could use a spinal tap to look directly at the amount of A-beta present in the cerebrospinal fluid, but we've shown that natural processes cause A-beta levels to change dynamically," says Bateman. "Such changes make it more difficult to assess the effects of a drug in that fashion."

The study was funded through a Lilly grant from a funding program that allowed Bateman to propose the research and retain control of it. Five of the paper's 12 authors are Eli Lilly employees.

Washington University in St. Louis licensed its pending patents on SILK to C2N Diagnostics, LLC, a St. Louis diagnostics company started by Bateman and senior author David Holtzman, M.D., the Andrew and Gretchen Jones Professor and Chair of Neurology. Bateman and Holtzman's financial interests in the company are governed by the university's conflict-of-interest policies.

Bateman RJ, Siemers E, Mawuenyega KG, Wen G, Bronwing KR, Sigurdson, WC, Yarasheski KE, Friedrich SW, DeMattos RB, May PC, Paul SM, Holtzman DM. A gamma-secretase inhibitor decreases amyloid-beta production in the central nervous system. Annals of Neurology, online April 10.

Funding from Eli Lilly and Company supported this research.

Omega-3 Fatty Acids May Benefit Cancer Patients Undergoing Major Operations

New research from Trinity College Dublin published in this month's Annals of Surgery points to a potentially significant advance in the treatment of patients undergoing major cancer surgery. The study was carried out by the oesophageal research group at Trinity College Dublin and St James's Hospital. A randomised controlled trial showed omega-3 fatty acids given as part of an oral nutritional supplement resulted in the preservation of muscle mass in patients undergoing surgery for oesopahageal cancer, a procedure normally associated with significant weight loss and quality of life issues.

The trial was designed by Professor John V Reynolds, Professor of Surgery at Trinity College Dublin and St James's Hospital, Dublin, and Dr Aoife Ryan PhD, a research dietitian at St James's Hospital, Dublin*.

Omega 3 fats are essential fats found naturally in oily fish, with highest concentrations in salmon, herring, mackerel, and sardines. Recently food manufacturers have begun to add omega 3 to foods such as yogurt, milk, juice, eggs and infant formula in light of a body of scientific evidence which suggests that they reduce cardiovascular disease risk, blood pressure, clot formations, and certain types of fat in the blood.

Previous studies had found that nutritional supplements containing one form of omega 3 fat, eicosapentaenoic acid (EPA), significantly reduced weight loss among inoperable cancer patients. The researchers hypothesised that a nutritional supplement rich in calories and a high dose of EPA would stem the debilitating weight loss seen in patients following oesophageal surgery. The group chose to study patients undergoing surgery for oesophageal cancer as this surgery is one of the most stressful and serious operations a patient can undergo.

Professor John V Reynolds, Professor of Surgery at TCD and St James's Hospital and the lead researcher on the study said: "There are almost 450 new cases of oesophageal cancer diagnosed every year in Ireland and Ireland has one of the highest rates of oesophageal cancer in Europe. An increasing number of patients are treated with chemotherapy alone or in combination with radiation therapy before they undergo surgery. The surgery is a serious operation lasting several hours and can take weeks to recover from surgery and up to six months to recover pre-illness quality of life. Weight loss is extremely common both before and especially after this type of surgery, and any approach that can preserve weight, in particular muscle weight and strength, may represent a real advance".

In a double-blinded randomised control trial, the gold standard in medical research, patients awaiting oesophagectomy surgery were randomly assigned to treatment and control groups. While both groups received a 240ml nutritional supplement twice daily starting five days before surgery (which was identical in calories, protein, micronutrients and flavor), patients in the treatment group received an enriched formula with omega 3 (2.2 gram EPA/day). Immediately following surgery, the supplement was given through a feeding tube for 14 days while patients recovered in hospital. Once patients could resume oral feeding, they continued drinking the supplement until 21 days post surgery.

Results:

The oesophageal research group at Trinity College Dublin and St James's Hospital found that patients given the standard feed (without omega 3) suffered clinically severe weight loss post surgery – losing an average of 4 lbs of muscle mass post surgery, where as in the omega 3 group patients maintained all aspects of their body composition

Commenting on the significance of the results, Dr Aoife Ryan said: "The results were extraordinary in the sense that no previous nutritional formulation had revealed such an outcome, with supplemented patients maintaining all aspects of their body composition in the three weeks following surgery. Patients given the standard supplement without omega 3 lost a significant amount of weight comprising 100% muscle mass. In fact 68% of patients suffered 'clinically severe' weight loss post surgery in the standard group (without omega 3) versus only 8% in the omega 3 group. The significant finding was that the patients did not lose just fat, as one would expect with weight loss, but instead they depleted their muscle stores significantly. Research has shown that a loss of 5lbs of weight produces significant effects on quality of life and a patient's ability to mobilise and perform simple activities of daily living. Losing 4 lbs of muscle is even more significant".

Professor John Reynolds said: "Omega 3 enriched nutrition appears to prevent loss of muscle mass by reducing the amount of inflammatory markers in the blood – this means the metabolism is not as stressed as it usually is post surgery. We also saw that the omega 3 group was less likely to have a fever in the first week post surgery which points to the ability of omega 3 to suppress inflammation. Looking at their blood tests omega 3 fed patients had much lower 'inflammatory compounds' circulating in their blood which points to the ability of omega 3 to reduce inflammation".

Using specialised nutritional feeds with a highly purified form of EPA, the researchers were able to administer a dose of omega 3 that was much higher than that typically found in food. They noted that treatment with omega 3 enriched supplement is only slightly more expensive than traditional nutritional therapy, and previous studies have yielded significant cost-savings in the form of fewer complications following surgery using immuno-nutrition feeds similar to this. "Initial treatments like this may be cost-effective for our cash-strapped health care system", said Dr Ryan.

Commenting in an accompanying editorial in the Annals of Surgery Dr Michael Meguid, Professor of Surgery at State University of New York noted: "This study is a significant step forward because it underscores the message to surgeons of the importance of using omega 3 based nutrition as an adjunct therapy started at least 5 days before surgery. It should no longer be a surgeon's preference, but the standard of expected norm for the practice of elective complex gut cancer surgery".

In conclusion, Professor John Reynolds said: "This study has provided an interesting insight into how nutritional therapy can positively impact on the major stress of cancer surgery. More studies need to be done, in particular to address whether such approaches lead to more rapid recovery of quality of life, reduce complications, and improve outcomes. Throughout cancer care, many patients undergoing therapy nowadays have a combination of surgery, chemotherapy and radiation therapy, and studies addressing whether nutritional supplementation with omega 3 for the entire duration of treatment should be considered. Finally, we do not expect these findings are unique to cancer surgery, and similar benefits may accrue to patients needing complex surgical care for non-cancer problems, for instance liver transplantation or major cardiac surgery."

For media queries contact TCD Press Officer, Caoimhe Ní Lochlainn, tel: 8962310\087-9958014. Professor John V Reynolds and Dr Aoife Ryan are available for interview on request.

Notes to Editor:
1.Full title of the Annals of Surgery article: "Enteral Nutrition Enriched with Eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double blinded randomized controlled trial". Authors: Aoife Ryan, John V Reynolds, Laura Healy, Miriam Byren, Jennifer Moore, Niamh Brannelly, Aisling McHugh, Deirdre McCormack, Philomena Flood.
2. Dr Aoife Ryan PhD, a research dietitian at St James's Hospital, Dublin has since taken up an appointment as Assistant Professor of Nutrition at New York University.
3. This trial was supported by a research grant from Abbott Laboratories

Is dark energy getting weaker?

* 10 April 2009 **by Rachel Courtland**

AFTER billions of years of runaway expansion, is the universe starting to slow down? A new analysis of nearby supernovae suggests space might not be expanding as quickly as it once was, a tantalising hint that the source of dark energy may be more exotic than we thought.

For more than a decade, astrophysicists have grappled with evidence of a baffling force that seems to be pushing the universe apart at an ever-increasing rate. Exactly what constitutes the dark energy responsible for this cosmic speed-up is unknown, says Michael Turner at the University of Chicago. "The simplest question we can ask is 'does the dark energy change with time?'"

So far, the evidence has suggested that dark energy is constant, though its effect on the universe has become stronger as the universe has expanded and the gravitational force between objects weakens with distance.

Now an analysis of supernovae suggests dark energy may actually be on the wane. In a paper on the physics preprint website, a team led by Arman Shafieloo at the University of Oxford examined a newly released catalogue of supernova explosions, including a number of relatively recent blasts nearby (www.arxiv.org/abs/0903.5141). They found that the new data made the best fit with a universe in which dark energy is losing strength. "It seems acceleration is slowing down," says Shafieloo.

The first evidence of dark energy emerged in 1998, when two teams of astronomers spotted distant supernova explosions that appeared dimmer than expected, and so further away. The find suggested the exploding stars were receding from Earth faster than anticipated, and therefore so was the rest of the universe. "Dark energy" was invoked to explain the apparent anomaly. Since then more supernovae have been catalogued to help build up a picture of how the universe has expanded over time.

The biggest set of supernova data was released earlier this year by the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts. It includes data on 147 supernovae that exploded in the last billion years, more than half of them newly discovered (www.arxiv.org/abs/0901.4787). The Harvard team analysed the new supernovae assuming that dark energy has remained unchanged.

Shafieloo, however, dropped the requirement that dark energy be constant over the universe's history. Together with Varun Sahni of the Inter-University Centre for Astronomy and Astrophysics in Pune, India, and Alexei Starobinsky of the Landau Institute for Theoretical Physics in Chernogolovka, Russia, Shafieloo used an approach he says is particularly sensitive to rapid changes in the universe's rate of expansion.

Beginning with factors like red shift - a measure of how much the expansion of space has stretched the light from each explosion - they calculated a representative number for the epoch in which each supernova occurred. After plotting all of these numbers, they found that the best fit was a scenario in which dark energy has weakened over the last 2 billion years, causing cosmic acceleration to slow down. Shafieloo cautions that their result is preliminary, but adds that it could be time to begin revisiting other models of dark energy.

"Their approach is reasonable," though the effect is slight, says cosmologist Dragan Huterer of the University of Michigan, Ann Arbor. "If that is really the case it would be a tremendous discovery."

Indeed, it would change our ideas about the source of dark energy. Until now, all signs have pointed to the cosmological constant as the simplest explanation for the accelerating expansion of the universe. This constant is an unchanging energy that arises from quantum fluctuations in the vacuum of space. "The cosmological constant is the only thing that makes any sense to particle physicists right now," says Huterer.

Yet if dark energy is changing, the cosmological constant could not be the driver. Instead, it would suggest far more exotic physics at work. It might even mean dark energy does not exist at all (see "We don't need the stuff"). One example of an exotic origin is "quintessence", a theoretical quantum field that permeates space like the as-yet-unidentified field thought to have driven inflation right after the big bang. This field could be dissipating and losing energy, eventually causing the universe to decelerate and collapse back on itself.

A more likely explanation for the team's result is a slight bias in the new supernova data, Huterer says. Robert Kirshner, a member of the Harvard team, agrees. "I think these are serious people whose analysis should be taken seriously, but there can be more than one cause for the apparent effect," he says.

For example, a potential bias could have been introduced thanks to dimmer objects being easier to see if they are nearby. It is possible that the Harvard team happened to catalogue a disproportionate number of nearby supernovae that were faint or obscured by dust. Astronomers must correct for the dimming effect of dust and other subtleties in order to estimate a supernova's true peak brightness. But the team may have overcompensated in this correction, producing a catalogue of nearby supernovae that are slightly too bright for their distance. That would create the illusion that the universe's acceleration has been slowing.

New observations from other groups need to be examined to look for the same effect, Kirshner says, though determining whether dark energy really is changing could take a while. The fine details of so many supernovae have been recorded that the so-called "systematic floor" has been hit - a scenario in which everything from subtle differences between supernova explosions to the warp of a telescope mirror can skew results, Huterer says.

Upcoming "precision projects" like the Dark Energy Survey, which will mount a supersensitive 500-megapixel camera on a 4-metre telescope at the Cerro Tololo Inter-American Observatory in Chile, aim to reduce some of the sources of uncertainty. One of the project's aims is to measure some of the universe's most recent history, by recording about 2000 supernovae that have exploded in the last 7 billion years.

Other probes that will push the limit in sensitivity are still in early planning, including two space probes - the US's Joint Dark Energy Mission and Europe's Euclid. Some astronomers suspect a partnership will be forged between these missions to send up a single international probe instead.

It is practically impossible to definitively discover if dark energy is constant. "There isn't a target to shoot for," says cosmologist Sean Carroll of Caltech. "As we narrow down the error bars and get closer and closer to perfectly constant, there's no point at which you say 'OK. We're done. Dark energy is constant.'"

However, the next burst of effort could reveal in glowing detail if dark energy has been changing. "It would be a surprise if we found that dark energy were varying with time," says Carroll, "but it would be so hugely important that it's still worth looking."

We don't need the stuff

Some theories claim to explain the universe's accelerating expansion without resorting to dark energy.

Some have it that cosmic acceleration is the result of the breakdown of general relativity in which space is forced apart at large scales. If that were the case, discrepancies should show up between measurements of the universe's expansion and the number of galaxy clusters, which is used to gauge how easily the universe can grow large structures. Such evidence has been lacking.

What's more, most such theories have a hard time explaining the acceleration of the cosmos without introducing other effects, such as instabilities that could preclude the formation of stars and galaxies. "None of the ideas make everything snap into place," says Sean Carroll of Caltech.

Another possibility is that matter is not uniformly distributed over large scales, and that the Earth is inside a vast bubble of space that is relatively devoid of matter. Gravity would have less pull in such a bubble, so it would expand rapidly. This expansion would affect light as it reached us from supernovae, meaning that they only appear to be moving away from us increasingly quickly, and that dark energy need not be invoked.

This scenario seems unlikely, says Alexei Starobinsky of the Landau Institute for Theoretical Physics in Chernogolovka, Russia. But the opposite - a smaller region with a slight excess of matter - could create a tug that would look like dark energy weakening of late. "That could explain this difference," he says.

Molecule prompts damaged heart cells to repair themselves after a heart attack

DALLAS - A protein that the heart produces during its early development reactivates the embryonic coronary developmental program and initiates migration of heart cells and blood vessel growth after a heart attack, researchers at UT Southwestern Medical Center have found.

The molecule, Thymosin beta-4 (TB4), is expressed by embryos during the heart's development and encourages migration of heart cells. The new findings in mice suggest that introducing TB4 systemically after a heart attack encourages new growth and repair of heart cells. The research findings indicate that the molecule affects developmental gene expression as early as 24 hours after systemic injection. The UT Southwestern study is online and will appear in an upcoming issue of the Journal of Molecular and Cellular Cardiology.

Drs. J. Michael DiMaio and Ildiko Bock-Marquette have found in mice that the molecule Thymosin beta-4 affects developmental gene expression in heart cells as early as 24 hours after systemic injection. The new findings suggest that introducing TB4 after a heart attack encourages new growth and repair of these cells.

"This molecule has the potential to reprogram cells in the body to get them to do what you want them to do," said Dr. J. Michael DiMaio, associate professor of cardiothoracic surgery at UT Southwestern and senior

author of the study. “Obviously, the clinical implications of this are enormous because of the potential to reverse damage inflicted on heart cells after a heart attack.”

Tremendous medical progress has been made to counter the damaging effects of heart attacks, but ordinarily, mammalian hearts are incapable of repairing themselves following damage. They are also limited in their ability to form new blood vessels. Earlier studies demonstrated that TB4 is expressed in the embryonic heart and stimulates cardiac vessels to form. It was therefore thought that introduction of TB4 might activate new vessel growth in the adult heart.

In this mouse study researchers found that TB4 initiates capillary tube formation of adult coronary endothelial cells in tissue culture. The molecule also encourages cardiac regeneration by inhibiting death in heart cells after an injury such as a heart attack and by stimulating new vessel growth.

“We observed that by injecting this protein systemically, there was increased cardiac function after a heart attack,” said Dr. Ildiko Bock-Marquette, assistant professor of cardiothoracic surgery at UT Southwestern and the study’s lead author. “We hope this protein can inhibit cell death that occurs during a heart attack in the short term, and that it may initiate new growth of coronary vessels by activating progenitor cells in the long term.”

Researchers assessed the effect of TB4 on new vessel growth in adult mice after inducing heart attacks and then following up by introducing TB4 into the animals. An examination of the capillary smooth muscle cells following treatment with TB4 showed a significant increase in capillary density in the heart three days afterward near the site of the heart attack, the scientists reported.

Further studies will examine whether the same events occur in larger mammals and which receptors are responsible for the action of this molecule.

Other UT Southwestern researchers involved in the study were Santwana Shrivastava, research assistant; and John Shelton, senior research scientist. Study authors also included Dr. Teg Pipes, former postdoctoral fellow; Jeffrey Thatcher, a doctoral candidate in biomedical engineering; Dr. Cristi Galindo, postdoctoral research fellow; and co-senior author, Dr. Eric Olson, chairman of molecular biology.

The work was supported by the Ted Nash Long Life Foundation, the American Heart Association, and the National Institutes of Health.

Visit http://www.utsouthwestern.org/heartlungvascular to learn more about UT Southwestern’s clinical services in cardiology and cardiothoracic and vascular surgery.

In the ICU, use of benzodiazepines, other factors may predict severity of post-stay depression

Psychiatrists and critical care specialists at Johns Hopkins have begun to tease out what there is about a stay in an intensive care unit (ICU) that leads so many patients to report depression after they go home.

In a study reported online April 10 in Critical Care Medicine, the Hopkins researchers say several factors predicted symptoms of depression six months after hospitalization among very sick ICU patients, including a high level of organ failure and being given relatively high doses of a benzodiazepine sedative.

"The hope is that as we learn more about the effect of variations in ICU care, we'll be able to predict which patients are most susceptible to depression, prevent some depression by changing ICU practices, and make sure patients receive adequate mental health monitoring after discharge," says O. Joseph Bienvenu, M.D., Ph.D., an associate professor in the Department of Psychiatry at the Johns Hopkins University School of Medicine.

Bienvenu says doctors have long theorized that a health problem devastating enough to send someone to an ICU might well trigger depression, but because only some patients become depressed, he and his colleagues wondered whether the root causes might be more complex.

"Historically, the only goal for critical care physicians, understandably, was to keep people alive, but now there is interest in longer-term outcomes, such as patients' mental health and well-being," says Bienvenu. "So we asked ourselves, could certain aspects of critical illness and ICU care swing patients toward depression?" To test the idea, Bienvenu and other Johns Hopkins researchers evaluated patients recently admitted to one of 13 ICUs located at four teaching hospitals in Baltimore, Md., including four ICUs at The Johns Hopkins Hospital.

Each of the patients was treated for acute lung injury (ALI), a respiratory distress syndrome that's considered an archetype of critical illness. Patients with ALI typically require invasive interventions in the ICU, including use of ventilators. Though better care has greatly reduced mortality rates, ALI still kills about 40 percent of those affected.

Bienvenu and his colleagues followed 160 patients who had survived at least six months after their ALI diagnosis. The researchers took note of a variety of features of each patient's status and care while in the ICU, such as severity of organ failure, their blood sugar levels and other lab work, and the amount and type of sedative they received.

At six months after ALI diagnosis, the researchers administered a questionnaire to patients that measured depressive symptoms ranging from none to possible or probable clinical depression. Of the 160, 26 percent scored above the threshold for possible depression. Compared to other ALI survivors, the depressed patients were more likely to have suffered greater severity of organ failure and to have received 75 mg or more of a benzodiazepine sedative daily.

Bienvenu says that because more severe organ failure may lead to a longer physical recovery period after ICU discharge, patients' depression may be explained, in part, by a slow recovery. However, he and his colleagues aren't sure how to explain the association between depression and ICU benzodiazepine dose.

One possibility could be that the amount of this drug received reflects how agitated patients were in the ICU, with very distressed individuals getting higher doses. However, because this relationship hasn't been seen with other types of sedatives commonly prescribed in the ICU, it's possible that high doses of benzodiazepine alone may somehow cause depressive symptoms. "This is clearly a question that needs further study," says Bienvenu.

Other Hopkins researchers who participated in this study include David W. Dowdy, M.D., Ph.D. (now in the Department of Medicine at the University of California, San Francisco), Victor D. Dinglas, B.S., Pedro A. Mendez-Tellez, M.D., Jonathan Sevransky, M.D., Carl Shanholtz, M.D., and Dale M. Needham, M.D., Ph.D.

CSHL-led team identifies key decision-point at which cells with broken DNA repair themselves or die

When cells undergo potentially catastrophic damage, for example as a result of exposure to ionizing radiation, they must make a decision: either to fix the damage or program themselves for death, a process called apoptosis.

It's a stark decision that is as mysterious as it is remarkable, involving what might be described metaphorically as a network of internal alarms that detect damage to DNA packed tightly in the cell nucleus. In intricate ways, cells orchestrate a response to signals from such resident sensors when they are triggered by exposure to radiation or other toxic processes, which if unchecked can cause genes to mutate and cancerous tumors to begin forming.

A team of biologists led by Professor Nicholas Tonks, Ph.D., F.R.S., of Cold Spring Harbor Laboratory (CSHL), this week revealed results of experiments suggesting at least one way in which cascades of intracellular signals are regulated at what they call a decision point – as cells decide whether to repair broken DNA strands or commit suicide following DNA damage.

In a report published online ahead of print in the Journal of Biological Chemistry, Tonks and colleagues identify a protein with the unlikely name Eyes Absent, or EYA, as performing a critical role in setting the damage-repair machinery in motion. Engaged within the larger context of a complex signaling cascade within the cell, EYA regulates the formation of specialized microenvironments on DNA, called gamma-H2A.X foci, which allow the cell to summon repair enzymes to the site of broken DNA strands. The team's experiments, conducted by Navasona Krishnan, Ph.D., of the Tonks lab, showed that when Eyes Absent was not present in damaged cells grown in culture, such foci were not formed and the cells went the route of apoptosis - they programmed themselves to die.

'A lovely moment' of discovery

Tonks says the finding is "a powerful example of multiple lines of research and different kinds of expertise coming together" in what he describes as "a lovely moment" of synthesis and discovery. An important collaborator in the work, C. David Allis, Ph.D., of the Rockefeller University, had recently published a paper in Nature describing a critical component of the DNA damage-repair signaling cascade. The Tonks-Allis collaboration, along with contributions from Seung Jun Kim, Ph.D., a protein crystallographer from the Korea Research Institute of Bioscience and Biotechnology, led to the assembly of a puzzle from pieces whose precise relation was not previously understood.

The parts of the puzzle include a protein called H2A.X, one of a species of proteins called histones that form structures around which DNA is "spooled" for dense packing in the cell nucleus. "David Allis showed us that this particular histone, which is found at those critical decision points called gamma-H2A.X foci, has phosphate groups added to its structure at particular points at the end of the protein. David demonstrated that another kind of protein - a kinase called WSTF - attaches phosphate to critical site, a tyrosine residue, at the extreme end of the protein," Tonks explains..

"I was interested in the fact that when there is damage to double-stranded DNA – catastrophic damage, such as when the strand breaks in two – the phosphate molecule placed at the decision point by WSTF has to be removed in order for the cell to send out signals for DNA-repair enzymes to come to the scene."

The removal of phosphate groups from proteins is accomplished by a family of enzymes called phosphatases – the focus of much research in Tonks' CSHL laboratory. Tonks is well known for having characterized the first of what has come to be understood as a large superfamily of protein tyrosine phosphatases, or PTPs – enzymes

that specifically remove phosphate molecules from amino acid residues called tyrosines. This function is critical in regulating cellular signaling in normal and disease conditions. In effect, important kinds of cellular signals can't be sent without helper enzymes like PTPs that remove phosphate molecules from specific locations, and kinase enzymes that perform the reverse role – that of adding phosphates.

Another vital piece of the puzzle in the current work involves Dr. Kim, who recently spent 15 months in the Tonks lab at CSHL, working on growing crystals of protein phosphatases to determine their structure, including that oddly named protein, Eyes Absent. Why that one? As Tonks explains, "EYA is known from work on the fruit fly, or Drosophila, to be a very unusual protein: it's the only one we know of that acts in the cell nucleus to regulate genes – what we call a transcription factor – while, in other contexts, is also known to act as a phosphatase – that is, it can remove phosphate groups from other proteins."

The role of Eyes Absent in DNA damage repair

EYA was shown to be a phosphatase by three separate groups in 2003. Although it was thought to be a PTP - i.e., it was thought to take phosphate groups off tyrosine residues in proteins - the identity of its target proteins in the cell was unknown. Kim's structure was important because it revealed a particular distribution of charged residues on the surface of the protein that suggested to Tonks the possibility that basic proteins, such as histone H2A.X, may be one such critical substrate.

This led to the experiments in which Tonks' team showed that Eyes Absent was in fact the protein that removed the critical phosphate group from the end of histone H2A.X, thereby allowing the formation of the so-called gamma-H2A.X foci, which set DNA repair in motion when double strands were broken. When EYA was experimentally "knocked out" via a technique called RNA interference, or RNAi, damaged cells with double-stranded DNA breaks did not repair themselves; instead, they simply died - underwent apoptosis.

As is often the case in science, multiple labs are engaged on related subjects. Results similar to those reported by Tonks and colleagues recently have been obtained in Geoff Rosenfeld's lab at the University of California, San Diego. But there is more work to be done of the subject. It remains unclear if or how the role of Eyes Absent in the DNA repair machinery - in other words, its role as a tyrosine phosphatase, or remover of phosphate molecules - is related to its role, in other contexts, as a transcription factor (a regulator of gene expression). It is certainly a curiosity that a protein that can regulate genes in certain contexts can act in others as the fulcrum in a mechanism that repairs damaged genes. Tonks and colleagues expect to explore this in future work.

"Dephosphorylation of the C-terminal tyrosyl residue of the DNA damage-related histone H2A.X is mediated by the protein phosphatase Eyes Absent (EYA)" appeared online ahead of print April 7 in the Journal of Biological Chemistry (http://www.jbc.org/cgi/doi/10.1074/jbc.C900032200). The full citation is: Navasona Krishnan, Dae Gwin Jeong, Suk-kyeong Jung, Seong Eon Ryu, Andrew Xiao, C. David Allis, Seung Jun Kim, and Nicholas K. Tonks.

Early land visitors borrowed shells for protection

* 10 April 2009 **by Jeff Hecht**

IT'S always good to have a bit of help to cross into the unknown. Some of the earliest creatures to crawl out of the ocean onto land half a billion years ago borrowed shells to carry a bit of the sea with them. This allowed them to survive in an otherwise hostile world, much like tanks of compressed air allow people to explore the deep ocean.

Palaeontologist James Hagadorn of Amherst College in Massachusetts has been studying fossilised tracks left in sandstone in central Wisconsin, dating back 490 to 510 million years. At the time, vast sandy tidal flats fluctuated between wet and dry zones, thrusting organisms into new environments.

Protichnites tracks from the late Cambrian, found in central Wisconsin **(Image: Joshua Gass)**

Hagadorn had determined that several sets of tracks were made by Protichnites, an arthropod with many pairs of legs crawling across the sand and dragging its tail behind. But some of the tracks show odd markings along their left side, as if the animals had bent tails that dragged to one side.

Hagadorn and Adolf Seilacher of Yale University now report that these tracks are very similar to the distinctive ones left by a hermit crab carrying a coiled shell. They conclude that the unusual tracks must belong to Protichnites that had partly inserted their tails into similar shells in order to carry them on land (Geology, vol 37, p 295).

Hauling shells would have given the critters an advantage. Trapped moisture protected them from drying out and helped keep their gills moist. The shells also shielded the animals from harsh ultraviolet light and protected them from changing temperatures.

Although the behaviour resembles that of a hermit crab, Hagadorn suspects these early explorers were the ancestors of a long-extinct group called sea scorpions, which had 6 to 13 pairs of legs. The tracks suggest the shells probably came from coiled molluscs, but other sources are possible. The hermit-like behaviour obviously had advantages, but the researchers say it is unclear how it came about. "We have no idea how this originated or what led to it," Hagadorn says.

Egg stem cells could revolutionise fertility treatment

* 18:00 12 April 2009 **by Linda Geddes**

The dogma that women are born with a finite number of eggs may soon be overturned. Stem cells have been discovered in the ovaries of adult mice that seem to give rise to new eggs and healthy offspring.

If these findings are confirmed, it could revolutionise female reproduction – opening the door for women to put off child-rearing almost indefinitely, and providing a new source of eggs for women who have been rendered infertile.

To isolate the mouse ovarian stem cells – dubbed female germline stem cells (FGSCs) – Ji Wu and his colleagues at Shanghai Jiao Tong University in China first looked for cells producing an egg-related protein called MVH in the ovaries of adult and five-day-old female mice. They then identified rapidly dividing cells and grew them in culture, where they continued to proliferate.

These FGSCs were injected into the ovaries of mice that had previously been sterilised by chemotherapy. Soon after, new eggs formed in the ovaries and the mice subsequently became pregnant and gave birth to healthy offspring. To confirm that the offspring really did come from the implanted eggs, Wu had inserted a gene encoding a fluorescent protein into the stem cells, which some of the offspring were also found to be carrying.

'Ultimate test'

"By producing live young, these cells have passed the ultimate test to prove their germline credentials," says Evelyn Telfer of the University of Edinburgh, UK. "It's very, very exciting."

Previous studies had hinted that ovaries or the bone marrow might contain stem cells capable of generating new eggs, but these findings were thrown into doubt when the eggs they generated couldn't be fertilised.

The next step will be for independent labs to replicate Wu's results – crucial, if they are to be accepted by the wider scientific community.

"Stem cell biology has been mired in the problem of replication, and a very high standard of proof is needed," says Roger Gosden of Weil Cornell Medical College in New York.

Burning question

If Wu has indeed identified FGSCs, the burning question is whether adult women also carry similar cells in their ovaries – and what the role of these cells might be in adults. Wu's study doesn't suggest that FGSCs produce new eggs in healthy adult ovaries, and the fact remains that female mice – and humans – experience a decline in eggs as they age.

"The fact that [FGSCs] are there doesn't mean they're doing anything," says Jonathan Tilly of Harvard Medical School, who first identified ovarian stem cell-like cells in 2004. "Perhaps these cells just shut down and that's why the ovaries fail."

Even if these cells have no role in adults, if they exist in humans and can be extracted, it would open the doors to growing large numbers of eggs in a dish to repopulate damaged or depleted ovaries, and create embryos for childless couples, or embryonic stem cell research. *Journal Reference: Nature Cell Biology (DOI: 10.1038/ncb1869)*

Diabetes 'impact on brain power'

Failure to control type 2 diabetes may have a long-term impact on the brain, research has suggested.

Severe hypoglycaemic episodes - hypos - occur when blood sugar levels drop dangerously low.

A University of Edinburgh team found they may lead to poorer memory and diminished brain power.

The study, based on 1,066 people with type 2 diabetes aged between 60 and 75, was presented at a conference of the charity Diabetes UK.

The volunteers completed seven tests assessing mental abilities such as memory, logic and concentration.

The 113 people who had previously experienced severe hypos scored lower than the rest of the group. They performed poorly in tests of their general mental ability, and vocabulary.

There are at least 670,000 people in England aged between 60 and 75 years old who have Type 2 diabetes and around a third of them could be at risk of a hypo.

HYPOGLYCAEMIA
Hypoglycaemia is caused by a lack of sugar (glucose) reaching the brain, which uses it as fuel
Symptoms can include sweating, fatigue, hunger, feeling dizzy, feeling weak, a higher heart rate than usual and blurred vision
More severe episodes can led to temporary loss of consciousness, convulsions and coma

Possible reasons

Lead researcher Dr Jackie Price said: "Either hypos lead to cognitive decline, or cognitive decline makes it more difficult for people to manage their diabetes, which in turn causes more hypos.

"A third explanation could be that a third unidentified factor is causing both the hypos and the cognitive decline. "We are carrying out more research to establish which explanation is the most likely."

Dr Iain Frame, director of research at Diabetes UK, said: "This study reinforces previous evidence which suggests that poorly controlled diabetes affects the functioning of the brain.

"We already know that type 2 diabetes increases the risk of developing Alzheimer's disease, which is a type of dementia, and this research adds another piece to a very complex jigsaw puzzle.

"However, more research is needed before we can come to any firm conclusions."

There are 2.5 million people diagnosed with diabetes in the UK and up to 500,000 who have type 2 diabetes but do not know it. It is predicted that by 2025 there will be up to four million people with diabetes in the UK.

Scientists find 'pleasure nerves'

Scientists say they understand more about how the body responds to pleasurable touch.

A team, including scientists from the Unilever company, have identified a class of nerve fibres in the skin which specifically send pleasure messages. And people had to be stroked at a certain speed - 4-5cm per second - to activate the pleasure sensation. They say the study, published in Nature Neuroscience, could help understand how touch sustains human relationships.

For many years, scientists have been trying to understand the mechanisms behind how the body experiences pain, and the nerves involved in conveying those messages to the brain. This is because people can suffer a great deal.

Neuropathy, where the peripheral nervous system is damaged, can be very painful and sometimes the messaging system goes wrong a people feel pain even when there is no cause.

Hairy skin

But the researchers involved in this work were looking to understand the opposite sensation - pleasure.

This research, which also involved experts at the University of Gothenburg in Sweden and at the University of North Carolina, recorded nerve responses in 20 people.

They then tested how people responded to having their forearm skin stroked at a range of different speeds.

They identified "C-tactile" nerve fibres as those stimulated when people said a touch had been pleasant.

If the stroke was faster or slower than the optimum speed, the touch was not pleasurable and the nerve fibres were not activated. The scientists also discovered that the C-tactile nerve fibres are only present on hairy skin, and are not found on the hand.

Professor Francis McGlone, now based at Unilever after an academic career where he carried out research into nerve response, says this is likely to be a deliberate "design". "We believe this could be Mother Nature's way of ensuring that mixed messages are not sent to the brain when it is in use as a functional tool."

He said the speed at which people found arm-stroking pleasurable was the same as that which a mother uses to comfort a baby, or couples use to show affection.

Professor McGlone said it was part of the evolutionary mechanism that sustained relationships between adults, or with children.

"Our primary impulse as humans is procreation, but there are some mechanisms in place that are associated with behaviour and reward which are there to ensure relationships continue."

'I can eat pizza again after 10 years'

By Jane Elliott Health reporter, BBC News

Ellie Banks loves her food, but for the last decade she has had chronic acid reflux (severe heartburn) and has had to watch what she eats.

Pizza has been out, so have spicy foods and even wine.

"I haven't been able to eat so many things," said the press officer, from Stoke.

Then at the end of last year Ellie was given surgery called a laparoscopic fundoplication.

Safer surgery

The operation involves wrapping a piece of the stomach around the oesophagus to create a new valve to prevent acid backing up from the stomach.

It used to be done by opening up the chest cavity, but with the advent of keyhole surgery it is now a lot safer.

There have been calls for the operation to be more widely available.

Ellie says the operation has transformed her life.

"I could just not get to sleep and kept waking up all night in absolute agony," she said. "If I had eaten pizza or had had wine or anything like that it would hurt like hell and I would bring the food up. It was really quite vile. 'I can eat pizza again after 10 years'

Taking action

"I saw loads of different doctors for about 10 years until they actually sent me to see a specialist. "They gave me some tablets, but said there was nothing they could do about it. "Because I was quite skinny and it is usually larger people who get it, they did not think I had the same problem.

"I cut down my drinking and started eating more healthily, but it did not make any difference.

"I did not want to be dependant on the tablets and did not like putting them into my body every day."

But Ellie said things moved very quickly when she went to see her new GP.

"He sent me for tests and then they put a tube down my nose and every time I ate I had to press a button to measure the acid. "They said the acid was horrendous and put me in for the operation

"It was completely life changing."

Ellie Banks can now eat pizza

Research data

NHS research by the University of Aberdeen recently found good results following surgery.

A year after keyhole surgery, only 14% of patients were still taking medication, compared with 90% of those treated with drugs alone.

A trial of 800 patients suggested that the surgery should now be done more routinely in patients with chronic acid reflux.

The results so far suggest the procedure, although expensive at £2,000 per patient, is cost-effective because reflux sufferers no longer have to take medication and their quality of life improves.

HEARTBURN
A painful and burning sensation in the oesophagus, just below the breastbone usually associated with regurgitation of gastric acid
It is a very common condition with 20% of the population experiencing it at some point in their lives
Those at the more severe end of the spectrum can end up taking tablets for the rest of their lives

But the researches are continuing to follow the patients for five years to check the benefits are long-term.

Professor Roger Jones, head of general practice at King's College London and chair of the Primary Care Gastroenterology Society, said he had a number of patients contacting him recently and asking for the surgery, but he said some GPs still knew little about the technique.

"I think it does not always cross GPs' minds that hospitals are doing this," he said.

"But it is quite an important message to get out to GPs that patients who require long-term treatment with severe symptoms this is something that they ought to consider."