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Research deciphers HIV attack plan

Scientists get inside look at how AIDS virus grooms its assault team

LOS ALAMOS, N. M. - A new study by Los Alamos National Laboratory and University of Pennsylvania scientists defines previously unknown properties of transmitted HIV-1, the virus that causes AIDS. The viruses that successfully pass from a chronically infected person to a new individual are both remarkably resistant to a powerful initial human immune-response mechanism, and they are blanketed in a greater amount of envelope protein that helps them access and enter host cells.

These findings will help inform vaccine design and interpretation of vaccine trials, and provide new insights into the basic biology of viral/host dynamics of infection.

During the course of each AIDS infection, the HIV-1 virus evolves within the infected person to escape the host's natural immune response and adapt to the local environment within the infected individual. Because HIV evolves so rapidly and so extensively, each person acquires and harbors a complex, very diverse set of viruses that develops over the years of their infection. Yet when HIV is transmitted to a new person from their partner, typically only a single virus from the diverse set in the partner is transmitted to establish the new infection. The key discoveries here are the specific features that distinguish those specific viruses which successfully move to the new host, compared with the myriad forms in the viral population present in a chronically infected individual.

"The viruses that make it through transmission barriers to infect a new person are particularly infectious and resilient," said Los Alamos National Laboratory scientist Bette Korber. "Through this study we now better understand the biology that defines that resilience."

The team set out to determine whether the viruses that were successfully transmitted to a new patient might share distinct biological properties relative to those typically isolated from people with long-term, chronic infection. To do this, the group at U Penn cloned a set of intact viruses from acute infection, and a set of viruses from chronically infected people, and characterized them by measuring quantities that might be related to the virus's ability to successfully establish a new infection. They discovered several clear correlations. For example, transmitted viruses were both more infectious and contained more protective "envelope" per virus; envelope is the protein the virus uses to enter host cells.

The team identified an additional interesting property that could be a general characteristic of new viral infections: the transmitted HIV was capable of replicating and growing well in the presence of alpha interferon. Alpha interferon production is part of our innate human immune response to a new infection. As soon as a new viral infection is initiated in our bodies, local immune cells at the site of infection start secreting molecules called cytokines that have general antiviral activity and can inhibit the production of the newly infected virus. Alpha interferon is one of these potent cytokines.

In the early days of an HIV infection, this innate immune response increases to an intense level, called a "cytokine storm," which gradually recedes during infection. For a newly transmitted HIV to successfully establish infection, it must grow and expand in the new host while facing this cytokine storm. Although typical chronic viruses are sensitive to and inhibited by alpha interferon, transmitted HIV-1 viruses grew well in the presence of interferon.

Los Alamos scientists Elena Giorgi, James Theiler and Bette Korber were part of the analysis team working closely with investigators at the University of Pennsylvania, Nick Parrish and Beatrice Hahn. The paper, "Phenotypic properties of transmitted founder HIV-1" is in this week's issue of Proceedings of the National Academy of Sciences.

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http://www.eurekalert.org/pub_releases/2013-04/wfbm-raf040113.php

Researchers are first to use common virus to 'fortify' adult stem cells

Potential uses of engineered cells include organ transplant and brain injury

WINSTON-SALEM, N.C. - Using the same strategy that a common virus employs to evade the human immune system, researchers at Wake Forest Baptist Medical Center's Institute for Regenerative Medicine have modified adult stem cells to increase their survival – with the goal of giving the cells time to exert their natural healing abilities.

"Basically, we've helped the cells be 'invisible' to the body's natural killer cells, T cells and other aspects of the immune system, so they can survive to promote healing," said Graca Almeida-Porada, M.D., Ph.D., senior author and professor of regenerative medicine at Wake Forest Baptist.

The research, reported in the current issue of PLOS One, a peer-reviewed, open access journal, involves mesenchymal stem cells (MSCs), found in bone marrow, peripheral and cord blood and fetal liver and lung

tissue. These cells are known for their ability to migrate to damaged tissues and contribute to healing. However, like all cells, they are susceptible to being killed by the body's complement system, a part of the immune system involved in inflammation and organ rejection.

"These cells have a natural ability to help modulate the immune response, so if we can increase their survival, they theoretically could be a therapy to decrease inflammation and help transplant patients avoid organ rejection," said Almeida-Porada.

In the study, the researchers evaluated the potential of human cytomegalovirus (HCMV), a member of the herpes virus family, to help increase the survival of MSCs. While the HCMV virus infects between 50 percent and 80 percent of people in the U.S., it normally produces no symptoms and remains latent in the body over long periods.

"We wanted to take advantage of the virus' ability to evade the immune system," said Almeida-Porada. "Our strategy was to modify the cells to produce the same proteins as the HCMV virus so they could escape death and help modulate inflammation and promote healing."

MSCs were purified from human fetal liver tissue. They were then engineered to produce specific proteins expressed by the HCMV virus. Through this process, the scientists identified the protein that was most effective at increasing cell survival. Specifically, the team is the first to show that overexpression of the US2 protein made the cells less recognizable to the immune system and increased cell survival by 59 percent (+/- 13 percent).

"The research showed that modifying the cells indeed improves their survival," said Almeida-Porada. "Next, we hope to evaluate the healing potential of these cells in conditions such as bowel disease, traumatic brain injury and human organ transplant."

The research was supported by National Institutes of Health grants HL73737 and HL97623.

Almeida-Porada's co-researchers were Melisa A. Soland, Ph.D., and Christopher Porada, Ph.D., Wake Forest Baptist; Mariana Bego, Ph.D., Institut de Recherches Cliniques de Montreal, Canada; and Evan Colletti, Ph.D., Esmail Zanjani, Ph.D., and Stephen S. Jeor, Ph.D., University of Nevada.

http://www.eurekalert.org/pub_releases/2013-04/aaon-ttp032713.php

Tests to predict heart problems may be more useful predictor of memory loss than dementia tests

Tools that estimate future risk of heart disease and stroke may be more useful predictors of future decline in cognitive abilities than a dementia risk score

MINNEAPOLIS – Risk prediction tools that estimate future risk of heart disease and stroke may be more useful predictors of future decline in cognitive abilities, or memory and thinking, than a dementia risk score, according to a new study published in the April 2, 2013, print issue of *Neurology*[®], the medical journal of the American Academy of Neurology.

"This is the first study that compares these risk scores with a dementia risk score to study decline in cognitive abilities 10 years later," said Sara Kaffashian, PhD, with the French National Institute of Health and Medical Research (INSERM) in Paris, France.

The study involved 7,830 men and women with an average age of 55. Risk of heart disease and stroke (cardiovascular disease) and risk of dementia were calculated for each participant at the beginning of the study. The heart disease risk score included the following risk factors: age, blood pressure, treatment for high blood pressure, high density lipoprotein (HDL) cholesterol, total cholesterol, smoking, and diabetes. The stroke risk score included age, blood pressure, treatment for high blood pressure, diabetes, smoking, history of heart disease, and presence of cardiac arrhythmia (irregular heart beat).

The dementia risk score included age, education, blood pressure, body mass index (BMI), total cholesterol, exercise, and whether a person had the APOE ε4 gene, a gene associated with dementia.

Memory and thinking abilities were measured three times over 10 years.

The study found that all three risk scores predicted 10-year decline in multiple cognitive tests. However, heart disease risk scores showed stronger links with cognitive decline than a dementia risk score. Both heart and stroke risk were associated with decline in all cognitive tests except memory; dementia risk was not linked with decline in memory and verbal fluency.

"Although the dementia and cardiovascular risk scores all predict cognitive decline starting in late middle age, cardiovascular risk scores may have an advantage over the dementia risk score for use in prevention and for targeting changeable risk factors since they are already used by many physicians. The findings also emphasize the importance of risk factors for cardiovascular disease such as high cholesterol and high blood pressure in not only increasing risk of heart disease and stroke but also having a negative impact on cognitive abilities," said Kaffashian.

The study was supported by Région Ile-de-France, the Medical Research Council, the British Heart Foundation, the Health and Safety Executive, the French Department of Health, the National Heart, Lung, and Blood Institute, the National Institutes of Health, National Institute on Aging, Agency for Health Care Policy Research and the John D. and Catherine T. MacArthur Foundation.

<http://www.sciencedaily.com/releases/2013/04/130401075241.htm>

Varicella Vaccine Has Long-Term Effectiveness Against Chicken Pox

Chicken pox has been largely neutralized by the varicella vaccine

Chicken pox, the childhood affliction of earlier generations, has been largely neutralized by the varicella vaccine, according to a new study by the Kaiser Permanente Vaccine Study Center, which appears in the current online issue of Pediatrics.

The 14-year study followed 7,585 children who were vaccinated in 1995, when they were 12 to 23 months old, to assess the long-term effectiveness of the vaccine and the impact on the epidemiology of varicella (chicken pox) and herpes zoster (shingles). Researchers also observed the impact of the second dose of varicella vaccine, introduced in 2006.

The varicella vaccine was licensed in the United States in 1995, and recommended soon after by the Advisory Committee on Immunization Practices for routine administration to children. Prior to that, chicken pox was ubiquitous, with more than 90 percent of young people experiencing infection by the age of 20.

Over the entire follow-up period, the incidence rate of chicken pox in this cohort was 9 to 10 times lower than corresponding rates in unvaccinated children of the same age in the pre-vaccine era. This resulted in an overall vaccine effectiveness rate of approximately 90 percent.

"Clearly, the vaccine is a very effective tool in preventing or limiting the severity of chicken pox in young people," said Randy Bergen, MD, chief of outpatient pediatrics at Kaiser Permanente's Walnut Creek Medical Center and a pediatric infectious disease consultant. "As with any vaccine, though, the rate of vaccination has a huge impact on effectiveness. The more children vaccinated, the more effective the vaccine is for the entire community. At Kaiser Permanente, our use of a comprehensive electronic health record, Kaiser Permanente HealthConnect®, enables us to quickly identify children in the targeted age ranges who have not been vaccinated, and to reach out to their parents to ensure they get the shots. Keeping vaccination rates high confers benefit on the community as a whole because there are fewer children who can contract and spread the virus." A total of 1,505 breakthrough cases of chicken pox were reported within the study cohort of 7,585 children in the 14 years following varicella vaccination. "Breakthrough cases" are so named because they occur despite the child having received the varicella vaccine; the virus "breaks through" the defenses afforded by the vaccine. Cases were classified as "mild" (less than 50 lesions), "moderate" (51 to 300 lesions) and "severe" (more than 300 lesions). Very few cases were severe (only 28 of 7,585 children over 14 years), whereas in the pre-vaccine era most children experienced severe symptoms. Prevention of moderate to severe disease was achieved with one dose of varicella vaccine; no cases were reported after the second dose.

The incidence rate of breakthrough varicella steadily decreased over time and no increase was observed during the 14 years of follow-up. The apparent increase in the vaccine's effectiveness over time, according to lead author Roger Baxter, MD, co-director of the Kaiser Permanente Vaccine Study Center, "is likely the result of vaccine failure occurring early, while breakthroughs became rare due to high vaccine effectiveness both directly and through herd immunity."

The continuing decline in breakthrough rates observed in 2008 and 2009 may have been the result of the implementation of the second dose in 2006, researchers said. The second dose of varicella is typically given at ages 4 to 6 years. However, it could potentially be of more benefit if given early after the first dose -- if varicella is circulating -- by increasing protection for infants too young to receive the vaccine and immune-compromised children who cannot receive a live vaccine.

The risk of herpes zoster, commonly known as shingles, was not increased in vaccinated children, and appeared to be lower in vaccinated children than in the pre-vaccine era. There were 46 confirmed cases of shingles among the cohort, suggesting an approximately 40 percent decreased incidence of herpes zoster in vaccinated children.

Additional authors on the study include Paula Ray, MPH, Edwin Lewis, MPH, and Bruce Fireman, MA, with the Kaiser Permanente Vaccine Study Center; Patricia Saddier, MD, PhD, and Trung N. Tran, MD, PhD, of the epidemiology department, Merck Sharp & Dohme, Corp., Whitehouse Station, N.J.; Steve Black, MD, of the Center for Global Health, Cincinnati Children's Hospital, Cincinnati; Henry R. Shinefield, MD, of the University of California San Francisco Medical Center; and Paul M. Coplan, ScD, MBA, of Purdue Pharma, Stamford, Conn.

Trung Nam Tran, MD, and Paul Coplan were employees of Merck Sharp & Dohme, Corp. at the time of the study. Patricia Saddier, MD, is currently still an employee of Merck Sharp & Dohme, Corp. Roger Baxter, MD, has received research grants from Merck, Sanofi Pasteur, GSK and Novartis. Steve Black, MD, is a consultant for Novartis, and is on data safety monitoring boards for Novartis, GSK and the World Health Organization. All other authors report no conflicts of interest.

Roger Baxter, Paula Ray, Trung N. Tran, Steve Black, Henry R. Shinefield, Paul M. Coplan, Edwin Lewis, Bruce Fireman, and Patricia Saddier. Long-term Effectiveness of Varicella Vaccine: A 14-Year, Prospective Cohort Study. Pediatrics, 2013; DOI: 10.1542/peds.2012-3303

<http://www.sciencedaily.com/releases/2013/04/130401101027.htm>

New Type of Deadly Lymphoma Identified; Discovery Enables More Effective Treatment for Patients

An international research team has identified a new type of deadly intestinal lymphoma that is particularly common in Asia.

The team, led by clinician-scientists from the SingHealth Academic Healthcare Cluster, also developed a new diagnostic test to accurately identify these patients.

The study, carried out by the Singapore Lymphoma Study Group at Singapore General Hospital (SGH) and the National Cancer Centre Singapore (NCCS), has an immediate impact on patient care, with doctors now able to diagnose patients accurately and tailor more effective treatment strategies to improve outcomes. It will also impact the most recent WHO classification of haematolymphoid neoplasms.

This is the largest study of this lymphoma type, involving 60 cases from centres in Singapore and around Asia, including South Korea, Hong Kong, Taiwan, Australia, China and Malaysia. The findings were advanced published online in *Leukemia* earlier this month.

The disease, almost unheard of before 2008, has been classified as an alternative type of enteropathy-associated T-cell lymphoma (EATL Type I), a disease common in Caucasians and associated with coeliac disease.

"We discovered that the intestinal lymphoma commonly seen in Asian patients has no links to coeliac disease or EATL Type I found in Caucasians," said Associate Professor Tan Soo Yong, Senior Consultant, Department of Pathology at SGH, and first author of the study. "Instead, we discovered that the pathology of this disease is very different and most likely originates from a unique epithelial cell type found in the intestine, making it a completely different disease type."

"We, therefore, propose to re-classify the disease, currently labelled EATL Type II, as 'Epitheliotropic Intestinal T-cell Lymphoma' (EITL)," added Assoc Prof Tan, who is also Director of the SingHealth Tissue Repository and a faculty at Duke-NUS. This would impact the WHO's classification.

In addition, the team has identified a novel biomarker, known as MATK (megakaryocyte-associated tyrosine kinase), and developed a diagnostic test that enables clinicians to accurately diagnose patients suffering from this type of lymphoma. Requests for this test have come in from around the world, including China and the U.S. "Our research has an immediate impact on the care we can provide to patients with this rare but very aggressive intestinal lymphoma," said Associate Prof Lim Soon Thye, Deputy Head and Senior Consultant, Department of Medical Oncology, NCCS, and Associate Professor at Duke-NUS. "With an accurate diagnosis, we can treat our patients better and improve overall survival." The average overall survival observed by the researchers was only seven months.

The study is a testimony to the close collaboration between scientists, pathologists and clinicians in the Singapore Lymphoma Study Group and investigators from across the region. "It underscores the importance of working with a multidisciplinary team across institutions and countries to address gaps in research in Asia," added Assoc Prof Lim, who is the senior author of the study.

Expanding on the benefit of a multi-disciplinary approach, Professor Teh Bin Tean, Professor at NCCS and Duke-NUS, said: "One of the advantages of pursuing academic medicine is that we can approach questions seen at the bedside from all angles, avoiding a silo approach. And once we have results, the different team members bring this knowledge back to their different specialties -- to develop diagnostic kits, identify potential drug candidates or to implement changes to clinical practice."

Next, the researchers plan to collaborate with international experts in the United States and Canada to investigate the cell of origin and explore immunological approaches to block its growth.

The research was supported by grants from the National Medical Research Council (NMRC) of Singapore, SingHealth Foundation, and the HSBC Trustee (Singapore) Ltd as trustees of the Major John Long Trust Fund and the Chew Woon Poh Trust Fund.

S-Y Tan, S-S Chuang, T Tang, L Tan, Y-H Ko, K-L Chuah, S-B Ng, W-J Chng, K Gatter, F Loong, Y-H Liu, P Hosking, P-L Cheah, B-T Teh, K Tay, M Koh, S-T Lim. Type II EATL (epitheliotropic intestinal T-cell lymphoma): a neoplasm of intra-epithelial T-cells with predominant CD8 α phenotype. *Leukemia*, 2013; DOI: 10.1038/leu.2013.41

<http://www.sciencedaily.com/releases/2013/04/130401101021.htm>

Drug for Erectile Disorder Show Promise in the Treatment of Obesity

Sildenafil may also serve as a weight loss aid by coaxing our bodies to store more healthy "brown fat" than unhealthy "white fat"

Although sildenafil is best known for promoting erections, it may also serve as a weight loss aid by coaxing our bodies to store more healthy "brown fat" relative to unhealthy "white fat" than it would otherwise do on its own. According to new research published online in *The FASEB Journal*, this is because sildenafil inhibits the breakdown of cyclic GMP, which has been well known as a messenger molecule used by the body to control blood pressure and flow, and has now been shown to play an important role determining which type of fat -- white or brown -- the body stores.

"There is a growing need for novel treatments against obesity," said Alexander Pfeifer, M.D., Ph.D., a researcher involved in the work from the Institute of Pharmacology and Toxicology at the University of Bonn, Biomedical Center in Bonn, Germany. "Finding new positive effects of existing drugs, such as sildenafil, in adipose tissue might help to bridge the period until novel drugs against obesity have been developed."

To make this discovery, Pfeifer and colleagues used mice to show that cyclic GMP reduced the secretion of pro-inflammatory hormones, which, in turn, shifted the "color code" of fat from white to brown. Mice treated with sildenafil showed browning of the white fat after just a few days of treatment, which is believed to be the result of high cyclic GMP levels. Then the researchers used isolated fat cells and treated the cells directly with cyclic GMP and identified a "browning" effect as well.

"Clearly, size matters when it comes to our weight," said Gerald Weissmann, M.D., Editor-in-Chief of *The FASEB Journal*. "Numerous studies show that obesity is a risk factor for virtually every human disease, and that obesity is epidemic. The finding that Viagra® and similar drugs can change our body fat composition has major implications. These drugs have well defined risk/benefit profiles and are approved for the treatment of erectile disorders. Further research will determine whether they are useful in the treatment of human girth disorders."

<http://www.sciencedaily.com/releases/2013/04/130401111545.htm>

Nothing Fishy About It: Fish Oil Can Boost the Immune System

Fish oil rich in DHA and EPA is widely believed to help prevent disease by reducing inflammation, but until now, scientists were not entirely sure about its immune enhancing effects.

A new report appearing in the April 2013 issue of the *Journal of Leukocyte Biology*, helps provide clarity on this by showing that DHA-rich fish oil enhances B cell activity, a white blood cell, challenging the notion that fish oil is only immunosuppressive. This discovery is important as it shows that fish oil does not necessarily reduce the overall immune response to lower inflammation, possibly opening the doors for the use of fish oil among those with compromised immune systems.

"Fish oil may have immune enhancing properties that could benefit immunocompromised individuals," said Jenifer Fenton, Ph.D., M.P.H., a researcher involved in the work from the Department of Food Science and Human Nutrition at Michigan State University in East Lansing, Michigan.

To make this discovery, researchers used two groups of mice. One group was fed a control diet, and the other was fed a diet supplemented with DHA-rich fish oil for five weeks. B cells were harvested from several tissues and then stimulated in culture. Researchers then looked for markers of B cell activation on the cell surface, B cell membrane changes, and B cell cytokine production. They found that DHA-enriched fish oil enhanced B cell activation and select antibody production, which may actually aid immune responses associated with pathogen clearance, while possibly dampening the totality of the inflammatory response.

"This work confirms similar findings on fish oil and B cells from our lab, and moves us one step closer to understanding the immune enhancing properties of EPA and DHA," said S. Raza Shaikh, Ph.D., a researcher also involved in the work from the Department of Biochemistry and Molecular Biology at East Carolina University.

E. A. Gurzell, H. Teague, M. Harris, J. Clinthorne, S. R. Shaikh, J. I. Fenton. DHA-enriched fish oil targets B cell lipid microdomains and enhances ex vivo and in vivo B cell function. *Journal of Leukocyte Biology*, 2012; 93 (4): 463 DOI: 10.1189/jlb.0812394

http://www.eurekalert.org/pub_releases/2013-04/bu-mao040213.php

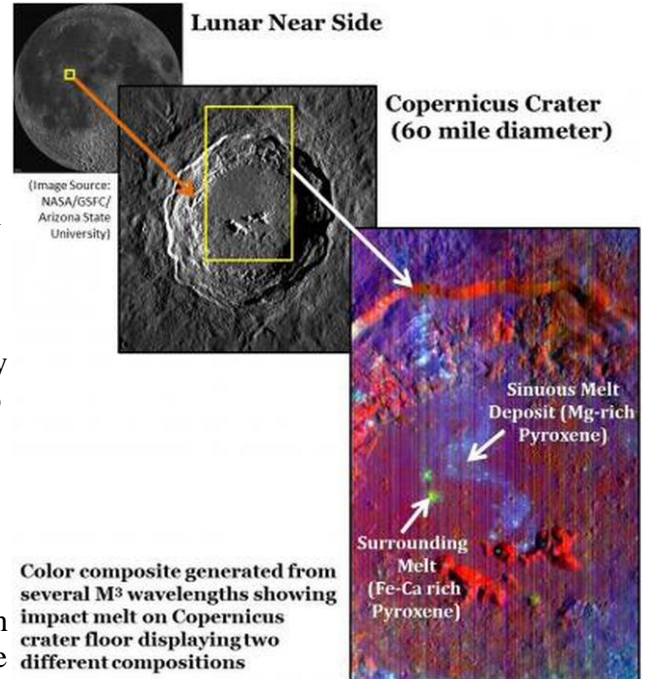
Mineral analysis of lunar crater deposit prompts a second look at the impact cratering process

Impacts on the Moon may not wipe the mineralogical slate clean

PROVIDENCE, R.I. [Brown University] — Despite the unimaginable energy produced during large impacts on the Moon, those impacts may not wipe the mineralogical slate clean, according to new research led by Brown University geoscientists. The researchers have discovered a rock body with a distinct mineralogy snaking for 18 miles across the floor of Copernicus crater, a 60-mile-wide hole on the Moon's near side. The sinuous feature appears to bear the mineralogical signature of rocks that were present before the impact that made the crater.

The deposit is interesting because it is part of a sheet of impact melt, the cooled remains of rocks melted during an impact. Geologists had long assumed that melt deposits would retain little pre-impact mineralogical diversity.

Large impacts produce giant cauldrons of impact melt that eventually cool and reform into solid rock. The assumption was that the impact energy would stir that cauldron thoroughly during the liquid phase, mixing all the rock types together into an indistinguishable mass. Identifying any pre-impact mineral variation would be a bit like dumping four-course meal into a blender and then trying to pick out the potatoes. But this distinct feature found at Copernicus suggests that pre-existing mineralogy isn't always blended away by the impact process.



Scientists had long assumed that large impacts on the Moon would wipe out any distinguishable mineralogy that was there before the impact. But a mineralogical feature discovered by

researchers at Brown University in *Copernicus crater shows that some of that mineralogy can survive. The results may force a rethinking of the cratering process.* NASA/Deepak Dhingra/Brown University

"The takeaway here is that impact melt deposits aren't bland," said Deepak Dhingra, a Brown graduate student who led the research. "The implication is that we don't understand the impact cratering process quite as well as we thought."

The findings are published in online early view in the journal *Geophysical Research Letters*.

Copernicus is one of the best-studied craters on the Moon, yet this deposit went unnoticed for decades. It was imaging in 83 wavelengths of light in the visible and near-infrared region by the Moon Mineralogy Mapper — M3 — that made the deposit stand out like a sore thumb.

M3 orbited the Moon for 10 months during 2008-09 aboard India's Chandrayaan-1 spacecraft and mapped nearly the whole lunar surface. Different minerals reflect light in different wavelengths at variable intensities. So by looking at the variation at those wavelengths, it's possible to identify minerals.

In the M3 imaging of Copernicus, the new feature appeared as an area that reflects less light at wavelengths around 900 and 2,000 nanometers, an indicator of minerals rich in magnesium pyroxenes. In the rest of the crater floor, there was a dominant dip beyond 950 nm and 2400 nm, indicating minerals rich in iron and calcium pyroxenes. "That means there are at least two different mineral compositions within the impact melt, something previously not known for impact melt on the Moon," Dhingra said.

It is not clear exactly how or why this feature formed the way it did, the researchers say. That's an area for future study. But the fact that impact melt isn't always homogenous changes the way geologists look at lunar impact craters.

"These features have preserved signatures of the original target material, providing 'pointers' that lead back to the source region inside the crater," said James W. Head III, the Scherck Distinguished Professor of Geological Sciences and one of the authors of the study. "Deepak's findings have provided new insight into the fundamentals of how the cratering process works. These results will now permit a more rigorous reconstruction of the cratering process to be undertaken."

Carle Pieters, a professor of geological sciences at Brown and the principle investigator of the M3 experiment, was one of the co-authors on the paper, with Peter Isaacson of the University of Hawaii.

http://www.eurekalert.org/pub_releases/2013-04/cmaj-tia032613.php

Tonsillectomy in adults with severe recurrent sore throats may benefit some people

Tonsillectomy may result in fewer severe sore throats and could benefit some adult patients, according to a randomized trial published in CMAJ (Canadian Medical Association Journal).

Recurrent severe sore throats result in lost work or school days and frequent use of antibiotics.

Researchers from Finland conducted a randomized open trial to determine whether tonsillectomy reduced episodes of severe sore throats (pharyngitis). The trial involved 86 patients, 46 of whom had the procedure and 40 who did not. The primary outcome was the difference in the number of patients with severe pharyngitis within 5 months. This had to be confirmed by a visit to a medical professional, a throat culture or blood sample and a rating of pain as severe.

At 5 months, 3% of the control patients (1) and none of the tonsillectomy group had a severe sore throat. Of the people in the tonsillectomy group, 4% (2) visited a physician for a severe sore throat compared with 43% (17) in the control group; 80% (32) of the control group had an acute sore throat compared with 39% (18) in the tonsillectomy group.

"During follow-up, the overall rate of pharyngitis and number of days with throat pain, fever, rhinitis and cough were significantly lower in the tonsillectomy group than in the control group," writes Dr. Timo Koskenkorva, Department of Otorhinolaryngology, Institute of Clinical Medicine, University of Oulu and Oulu University Hospital, Oulu, Finland, with coauthors. However, "patients in both groups graded their throat pain as mild." The tonsillectomy group reported improved quality of life with few lost work or school days compared with the control group. The researchers note that because the trial was open and participants knew whether they had had a tonsillectomy, subjective bias might have been introduced to the study.

"Adult patients who had disabling pharyngitis involving the palatine tonsils more than 3 times per year that prevented normal functioning and led to medical consultation benefitted from tonsillectomy," conclude the authors. "The morbidity and complications related to tonsillectomy must be considered when physicians and patients decide whether the clinical benefits outweigh the risks of surgery."

http://www.eurekalert.org/pub_releases/2013-04/lsh-lrd040213.php

LSUHSC research discoveries shed light on common STI

Common sexually transmitted infection-causing parasite "cultivates" bacteria beneficial to it

New Orleans, LA – Research led by David H. Martin, MD, Professor and Chief of Infectious Diseases at LSU Health Sciences Center New Orleans, has found that a common sexually transmitted infection-causing parasite "cultivates" bacteria beneficial to it, changing thinking about which comes first—infection or bacteria. The researchers also discovered a previously unknown species of these bacteria.

The research was published ahead of print online in Advance Access in the Journal of Infectious Diseases, and was published online April 2, 2013 in Research Highlights in Nature Reviews Urology.

Trichomonas vaginalis is a parasite and is a common sexually transmitted infection (STI) in women where it causes vaginal discharge, a higher rate of premature deliveries, and greater susceptibility to infection with the AIDS virus. Many women have this infection and do not know it.

It is known that a change in vaginal bacteria causes a problem known as bacterial vaginosis, and women with this condition are at increased risk of acquiring a trichomonas infection.

The researchers wondered if, among women with bacterial vaginosis, there were unique bacterial communities which would make women more susceptible to infection with trichomonas.

"We discovered that there are two unique bacterial communities that are very strongly associated with trichomonas infection," notes Dr. Martin. "In part what is unique about these communities is high concentrations of bacteria known as mycoplasmas. In fact one of these is a completely unknown bacterium which we have named Mnola because it is a mycoplasma discovered in NOLA."

The mycoplasma associated with the other unique bacterial community is Mycoplasma hominis, a well known bacterial pathogen. The data indicate that women with trichomonas and this unique bacterial community suffer from worse disease than the other trichomonas-infected women.

They have greater amounts of discharge and redness of the vaginal wall.

"We think that this group might also be at especially high risk for infection with HIV," adds Dr. Martin.

An especially interesting result of this research is that the evidence suggests that the trichomonas parasite is responsible in some way for the appearance these unique mycoplasma dominated bacterial communities.

"So instead of these unique communities predisposing a woman to infection as originally thought, we now believe that trichomonas takes on the role of a farmer in the vaginal environment by cultivating bacterial

communities that are in some way beneficial to itself. Proving this hypothesis and figuring out how these bacteria interact with trichomonas will be the subject of future research," concludes Dr. Martin.

Other members of the LSUHSC research team included Marcela Zozaya, Rebecca Lillis,

M. Jacques Nsuami, and Michael J. Ferris from the Section of Infectious Diseases in the Department of Medicine, the Department of Microbiology, Immunology & Parasitology, the Department of Pediatrics, and the Research Institute for Children.

The research was supported by grants from the National Institute of Allergy and Infectious Diseases and the Louisiana Board of Regents.

<http://phys.org/news/2013-04-longer-life-lithium-sulfur-batteries.html>

A longer life for lithium-sulfur batteries

This is an opportune time for a breakthrough in efficient and low-cost lithium-sulfur batteries.

Electric cars have still got it tough in the German marketplace. They are too expensive and their range is too short. This is an opportune time for a breakthrough in efficient and low-cost lithium-sulfur batteries.

There are currently over 40 million cars on Germany's roads. Only a fraction of them are powered by electric energy – around 6,400 vehicles according to the Federal Ministry of Transport, Building and Urban Development. The comparatively short range of electric cars doesn't help their popularity, with drivers often having to start the search for a charging station after a mere 100 kilometers, not to mention the high price of the batteries, which cost several thousand euros. Remediating this situation has researchers looking at new options in developing more efficient technologies. An extremely promising avenue of research is the lithium-sulfur battery, which is significantly more powerful and less expensive than the better-known lithium-ion battery. Although their short lifespan has made them unsuitable for use in cars before now, this may be about to change in the foreseeable future.

Scientists at the Fraunhofer Institute for Material and Beam Technology IWS in Dresden have developed a new design that increases the charge cycles of lithium-sulfur batteries by a factor of seven. "During previous tests, the batteries scarcely crossed the 200-cycle mark. By means of a special combination of anode and cathode material, we have now managed to extend the lifespan of lithium-sulfur button cells to 1,400 cycles," says Dr. Holger Althues, head of the Chemical Surface Technology group at IWS, who is delighted with his team's breakthrough. The anode of the team's prototype is not made from the usual metallic lithium, but from a silicon-carbon compound instead. This compound is significantly more stable, as it changes less during each charging process than metallic lithium. The more the structure of the anode changes, the more it interacts with the liquid electrolyte, which is situated between the anode and the cathode and carries the lithium-ions. This process causes the liquid to break down into gas and solids and the battery to dry out. "In extreme cases, the anode "grows" to reach the cathode, creating a short circuit and causing the battery to stop working altogether," explains Althues.

The interplay between anode and cathode is the critical factor determining the performance and lifespan of a battery. In the lithium-sulfur model, the cathode is composed of elemental sulfur. The advantage here is that unlike cobalt – the main cathode material used in lithium-ion batteries – sulfur is available in almost unlimited quantities and is therefore cheaper. The problem remains, however, that sulfur also interacts with the liquid electrolyte, which impairs the performance of batteries and, in the worst case, causes them to lose capacity entirely. The IWS researchers are using porous carbons to slow down this process. "We have precisely altered the pores to allow the sulfur to lodge there, slowing down the rate at which it combines with the electrolyte," clarifies Althues. He and his colleagues have developed a method of manufacturing these special cathodes. The experts at IWS measure the capacity of a battery in watt-hours per kilogram (Wh/kg). Over the long term, they expect lithium-sulfur batteries to reach an energy density of up to 600 Wh/kg. For comparison: the maximum energy density of the lithium-ion batteries currently in use is a mere 250 Wh/kg. "In the medium term, figures around the 500 Wh/kg mark are more realistic. In practical terms, this means you can drive twice as far with the same battery weight," says Althues. This of course implies that significantly lighter battery models are possible – an interesting prospect not only for automakers but for smartphone manufacturers too. After all, the overall weight of smartphones would be greatly reduced if they had lighter batteries. "Lithium-sulfur technology might even make electric flying a realistic possibility. Although such progress is still a long way off," adds Althues.

The researchers are currently working on further optimizing the material and using it in larger battery models. They are also turning their attention to suitable manufacturing methods. And with good reason, as this is the only way the technology will reach a mass market, leading to a significant increase in the number of electric cars on Germany's roads. *Provided by Fraunhofer-Gesellschaft*

<http://www.sciencedaily.com/releases/2013/04/130402090836.htm>

New Promise for an HIV Vaccine as Researchers Overcome Crucial Obstacle

For the first time, researchers stimulate immune cells that can produce broadly neutralizing antibodies

In a crucial step towards developing a successful HIV vaccine, researchers have been able, for the first time, to stimulate immune cells that can produce broadly neutralizing antibodies: a feat that has eluded vaccine researchers for decades. The exciting results are published in this month's issue of the Journal of Experimental Medicine.

It is widely accepted that a successful vaccine against HIV/AIDS would have to elicit antibodies to prevent infection from a wide spectrum of HIV strains. So far, no candidate vaccine for HIV has been able to produce such antibodies.

Leonidas Stamatatos, Andrew McGuire and their team of researchers at Seattle BioMed, in collaboration with colleagues at The Rockefeller University, the Scripps Research Institute and CalTech, wanted to understand why that was the case. A major goal of an HIV vaccine is to stimulate B cells to create antibodies that can effectively block HIV from entering a human host cell. The first generation of antibodies -- called "germline antibodies" -- are partially embedded in a B cell's membrane. If a germline antibody binds to a protein (called an "envelope protein") on the surface of HIV, even weakly, then the B cell is activated and begins producing antibodies not only on the surface of B cells, but also in the bloodstream. Activated B cells evolve to produce antibodies with even higher binding affinity to HIV, eventually resulting in a "mature" antibody. Some mature antibodies can bind to envelope proteins of many different HIV strains and prevent them from infecting cells. For this reason, these antibodies are called "broadly neutralizing antibodies." These are the antibodies a vaccine needs to elicit.

A small number of people infected with HIV naturally produce broadly neutralizing antibodies. By sequencing the DNA of their mature antibodies, Stamatatos and McGuire were able to deduce what the originating germline antibodies likely looked like. They then tested how well the mature and germline antibodies bound to the envelope protein of different HIV strains from around the world. Some of these envelope proteins have been tested previously as vaccine candidates, but they did not elicit broadly neutralizing antibodies. While the mature antibodies were able to bind 80-90% of these diverse envelope proteins, the germline antibodies did not bind at all. This indicated that a problem with previously tested HIV vaccines is that they do not bind to germline antibodies on B cells that ultimately give rise to mature, broadly neutralizing antibodies. Without this first binding step, the immune response to HIV is stopped before it can even truly begin.

Next, they turned to the structure of the HIV envelope proteins to determine why they were able to bind to the mature antibodies but not the germline. They discovered that several sugar molecules, called glycans, which HIV adds to its envelope protein to evade the immune system, were blocking the germline antibody from binding to and activating B cells.

After engineering an HIV envelope protein that lacks specific glycans, McGuire and Stamatatos ran their binding tests again. This time, the germline antibodies were able to bind the modified HIV protein. They also verified that the modified HIV protein was capable of starting the process of antibody maturation in B cells, kicking off an immune response that could eventually result in broadly neutralizing antibodies.

"We have overcome the first obstacle to elicit one type of anti-HIV broadly neutralizing antibodies through vaccination," explains McGuire. By administering the modified HIV protein as a vaccine, the immune system could become equipped to combat the real virus when it is encountered years down the line.

<http://www.sciencedaily.com/releases/2013/04/130402091133.htm>

The Hunt for the Creative Individual

Some people are more creative than others and are literally bubbling with ideas, while others rarely or never show signs of creativity. What should we look for when searching for creative people?

Creativity can quite simply be defined as the capacity to come up with new ideas to serve a purpose. Creativity is thus one of the most important sources of renewal. Creativity contributes to innovation and improvements in working life, commerce and industry.

No wonder employers want creative employees in areas where it is essential to come up with proposals for new products and services, and new ways of doing things.

The creative personality

Professor Øyvind L. Martinsen at BI Norwegian Business School has conducted a study to develop a personality profile for creative people: Which personality traits characterise creative people?

The study was conducted with 481 people with different backgrounds. The segment consists of various groups of more or less creative people.

The first group of creative people consists of 69 artists working as actors or musicians in a well-known symphony orchestra or are members of an artist's organisation with admission requirements.

The second group of creative people consists of 48 students of marketing.

The remaining participants in the study are managers, lecturers and students in programmes that are less associated with creativity than marketing.

The creativity researcher mapped the participants' personality traits and tested their creative abilities and skills through various types of tasks.

Seven creativity characteristics

In his study Martinsen identifies seven paramount personality traits that characterise creative people:

- **1. Associative orientation:** *Imaginative, playful, have a wealth of ideas, ability to be committed, sliding transitions between fact and fiction.*
- **2. Need for originality:** *Resists rules and conventions. Have a rebellious attitude due to a need to do things no one else does.*
- **3. Motivation:** *Have a need to perform, goal-oriented, innovative attitude, stamina to tackle difficult issues.*
- **4. Ambition:** *Have a need to be influential, attract attention and recognition.*
- **5. Flexibility:** *Have the ability to see different aspects of issues and come up with optional solutions.*
- **6. Low emotional stability:** *Have a tendency to experience negative emotions, greater fluctuations in moods and emotional state, failing self-confidence.*
- **7. Low sociability:** *Have a tendency not to be very considerate, are obstinate and find faults and flaws in ideas and people.*

Among the seven personality traits, associative orientation and flexibility are the factors that to the greatest extent lead to creative thinking. "Associative orientation is linked to ingenuity. Flexibility is linked to insight," says the professor. The other five characteristics describe emotional inclinations and motivational factors that influence creativity or spark an interest in creativity. "The seven personality traits influence creative performance through inter-action," Martinsen points out.

Less sociable

The study shows that the artists who participated scored much higher on associative orientation than the other participants. They have a substantial need for originality and are not particularly stable emotionally.

The personality profile of the marketing students was quite similar to the artist profile and also differs from the other participants in the study. The artists in the study also scored lower values for ambition than the others and are not particularly sociable either.

"An employer would be wise to conduct a position analysis to weigh the requirements for the ability to cooperate against the need for creativity," Martinsen believes. He also emphasises that creative people may need help to complete their projects. "Creative people are not always equally practical and performance-oriented, which is the reverse side of the "creativity medal."

Øyvind L. Martinsen. The Creative Personality: A Synthesis and Development of the Creative Person Profile. Creativity Research Journal, 2011; 23 (3): 185 DOI: 10.1080/10400419.2011.595656

<http://www.bbc.co.uk/news/science-environment-22005706>

Has Canada's government been muzzling its scientists?

Canada's Information Commission is to investigate claims that the government is "muzzling" its scientists.

Pallab Ghosh By Pallab Ghosh Science correspondent, BBC News

The move is in response to a complaint filed by academics and a campaign group. BBC News reported last year instances of the government blocking requests by journalists to interview scientists. Some scientists alleged that the muzzling could help suppress environmental concerns about government policies.

The former president of the Canadian Science Writers' Association, Veronique Morin, says that the commissioner's office will now have to find out if the federal government has in effect been operating a policy of censorship.

"Vital stories pertaining to the environment, natural resources, food safety, fisheries and oceans are not coming out in Canada because, for several years now, the government has imposed rules which prevents its scientists from speaking freely about their publicly funded research," she said.

"I am thrilled that the information commissioner has decided to take this on, and I am looking forward to the commission's report."

Canada's Globe and Mail newspaper reports that the Information Commission is investigating seven government departments: Environment, Fisheries and Oceans, Natural Resources, National Defence, the Treasury Board Secretariat, National Research Council of Canada and the Canadian Food Inspection Agency. The investigation is in response to a complaint filed by the University of Victoria's Environmental Law Centre (ELC) and the campaign group Democracy Watch.

Timely access

In a letter to the ELC, the assistant information commissioner, Emily McCarthy, stated her office is investigating possible violations of the Access to Information Act. "The commissioner has concluded that, to the extent that your complaint alleges that the right of access to information under the Act is impeded by government policies, practices or guidelines that restrict or prohibit government scientists from speaking with the media and the Canadian public, your complaint falls within the scope... of the Act," she said.

The ELC asked for an investigation into "the systematic efforts of the government of Canada to obstruct the right of the media - and through them, the Canadian public - to timely access to government scientists."

The report notes that the World Federation of Science Journalists (WFSJ) and the Canadian Science Writers' Association have both complained about the lack of "timely access" to government scientists.

Prof Jean-Marc Fleury, director of the WFSJ, said: "Canadian science journalists' fight against the Canadian government obstructing access to government researchers has finally achieved a major step forward."

The Canadian government has repeatedly denied allegations of muzzling rather a strict application of a "media protocol" set out by the governing Conservatives, shortly after their election in 2008.

The aim of the protocol, according to a leaked internal document, is to ensure that all messages from scientists are along "approved lines". The government's stated protocol is that ministers and senior civil servants should not be "surprised" by what they read in the newspapers.

<http://www.scientificamerican.com/article.cfm?id=just-a-theory-7-misused-science-words>

"Just a Theory": 7 Misused Science Words

From significant to natural, here are seven scientific terms that can prove troublesome for the public and across research disciplines

By Tia Ghose and LiveScience | Tuesday, April 2, 2013 | 89

Hypothesis. Theory. Law. These scientific words get bandied about regularly, yet the general public usually gets their meaning wrong.

Now, one scientist is arguing that people should do away with these misunderstood words altogether and replace them with the word "model." But those aren't the only science words that cause trouble, and simply replacing the words with others will just lead to new, widely misunderstood terms, several other scientists said. "A word like 'theory' is a technical scientific term," said Michael Fayer, a chemist at Stanford University. "The fact that many people understand its scientific meaning incorrectly does not mean we should stop using it. It means we need better scientific education."

From "theory" to "significant," here are seven scientific words that are often misused.

1. Hypothesis

The general public so widely misuses the words hypothesis, theory and law that scientists should stop using these terms, writes physicist Rhett Allain of Southeastern Louisiana University, in a blog post on Wired Science.

[\[Amazing Science: 25 Fun Facts\]](#)

"I don't think at this point it's worth saving those words," Allain told LiveScience.

A hypothesis is a proposed explanation for something that can actually be tested. But "if you just ask anyone what a hypothesis is, they just immediately say 'educated guess,'" Allain said.

2. Just a theory?

Climate-change deniers and creationists have deployed the word "theory" to cast doubt on climate change and evolution.

"It's as though it weren't true because it's just a theory," Allain said.

That's despite the fact that an overwhelming amount of evidence supports both human-caused climate change and Darwin's theory of evolution.

Part of the problem is that the word "theory" means something very different in lay language than it does in science: A scientific theory is an explanation of some aspect of the natural world that has been substantiated through repeated experiments or testing. But to the average Jane or Joe, a theory is just an idea that lives in someone's head, rather than an explanation rooted in experiment and testing.

3. Model

However, theory isn't the only science phrase that causes trouble. Even Allain's preferred term to replace hypothesis, theory and law -- "model" -- has its troubles. The word not only refers to toy cars and runway walkers, but also means different things in different scientific fields. A climate model is very different from a mathematical model, for instance.

"Scientists in different fields use these terms differently from each other," John Hawks, an anthropologist at the University of Wisconsin-Madison, wrote in an email to LiveScience. "I don't think that 'model' improves matters. It has an appearance of solidity in physics right now mainly because of the Standard Model. By

contrast, in genetics and evolution, 'models' are used very differently." (The Standard Model is the dominant theory governing particle physics.)

4. Skeptic

When people don't accept human-caused climate change, the media often describes those individuals as "climate skeptics." But that may give them too much credit, Michael Mann, a climate scientist at Pennsylvania State University, wrote in an email.

"Simply denying mainstream science based on flimsy, invalid and too-often agenda-driven critiques of science is not skepticism at all. It is contrarianism ... or denial," Mann told LiveScience.

Instead, true skeptics are open to scientific evidence and are willing to evenly assess it.

"All scientists should be skeptics. True skepticism is, as [Carl] Sagan described it, the 'self-correcting machinery' of science," Mann said.

5. Nature vs. nurture

The phrase "nature versus nurture" also gives scientists a headache, because it radically simplifies a very complicated process, said Dan Kruger, an evolutionary biologist at the University of Michigan.

"This is something that modern evolutionists cringe at," Kruger told LiveScience.

Genes may influence human beings, but so, too, do epigenetic changes. These modifications alter which genes get turned on, and are both heritable and easily influenced by the environment. The environment that shapes human behavior can be anything from the chemicals a fetus is exposed to in the womb to the block a person grew up on to the type of food they ate as a child, Kruger said. All these factors interact in a messy, unpredictable way.

6. Significant

Another word that sets scientists' teeth on edge is "significant."

"That's a huge weasel word. Does it mean statistically significant, or does it mean important?" said Michael O'Brien, the dean of the College of Arts and Science at the University of Missouri.

In statistics, something is significant if a difference is unlikely to be due to random chance. But that may not translate into a meaningful difference, in, say, headache symptoms or IQ.

7. Natural

"Natural" is another bugaboo for scientists. The term has become synonymous with being virtuous, healthy or good. But not everything artificial is unhealthy, and not everything that's natural is good for you.

"Uranium is natural, and if you inject enough of it, you're going to die," Kruger said.

Natural's sibling "organic" also has a problematic meaning, he said. While organic simply means "carbon-based" to scientists, the term is now used to describe pesticide-free peaches and high-end cotton sheets, as well.

Bad education

But though these words may be routinely misunderstood, the real problem, scientists say, is that people don't get rigorous science education in middle school and high school. As a result, the public doesn't understand how scientific explanations are formed, tested and accepted.

What's more, the human brain may not have evolved to intuitively understand key scientific concepts such as hypotheses or theories, Kruger said.

Most people tend to use mental shortcuts to make sense of the cacophony of information they're presented with every day.

One of those tendencies is to make a "binary distinction between something that is true in an absolute sense and something that's false or a lie," Kruger said. "With science, it's more of a continuum. We're continually building our understanding."

<http://www.sciencedaily.com/releases/2013/04/130402182454.htm>

New Genetic Evidence Suggests a Continuum Among Neurodevelopmental and Psychiatric Disorders

Research suggests that a broad spectrum of developmental and psychiatric disorders should be conceptualized as manifestations of a common underlying denominator, rather than independent conditions with distinct causes.

A paper published this month in the medical journal *The Lancet Neurology* suggests that a broad spectrum of developmental and psychiatric disorders, ranging from autism and intellectual disability to schizophrenia, should be conceptualized as different manifestations of a common underlying denominator, "developmental brain dysfunction," rather than completely independent conditions with distinct causes.

In "Developmental Brain Dysfunction: Revival and Expansion of Old Concepts Based on New Genetic Evidence," the authors make two key points:

• Developmental disorders (such as autism and intellectual disability) and psychiatric disorders (such as schizophrenia and bipolar disorder), while considered clinically distinct, actually share many of the same underlying genetic causes. This is an example of "variable expressivity:" the same genetic variant results in different clinical signs and symptoms in different individuals. • When quantitative measures of neuropsychological and neurobehavioral traits are studied instead of categorical diagnoses (which are either present or absent) and individuals are compared to their unaffected family members, it is possible to more accurately demonstrate the impact of genetic variants.

According to Andres Moreno De Luca, M.D., research scientist at the Autism and Developmental Medicine Institute at Geisinger Health System and article co-author, "Recent genetic studies conducted in thousands of individuals have shown that identical genetic mutations are shared among neurodevelopmental disorders that are thought to be clinically distinct. What we have seen over the past few years is that genetic mutations that were initially found in individuals with one disorder, such as intellectual disability or autism, are then identified in people with an apparently different condition like schizophrenia, epilepsy, or bipolar disorder."

"It turns out that the genes don't respect our diagnostic classification boundaries, but that really isn't surprising given the overlapping symptoms and frequent co-existence of neurodevelopmental disorders," said Scott M. Myers, M.D., autism specialist at Geisinger Health System and article co-author.

"We believe this study supports use of the term 'developmental brain dysfunction' or DBD, which would encompass the broad spectrum of neurodevelopmental and neuropsychiatric disorders," said David H. Ledbetter, Ph.D., executive vice president and chief scientific officer at Geisinger Health System, and article co-author.

"Additionally, it is clear that diagnostic tools such as whole genome analysis for both children and their families are essential when diagnosing and treating these disorders in order to ensure the most personalized treatment."

An example used in the study was analysis of intelligence quotient (IQ) scores. The average IQ score in the general population is 100. Historically, the medical community has defined intellectual disability as an IQ of less than 70 (with concurrent deficits in adaptive functioning). But according to Dr. Ledbetter, there is little difference in the function of a child with an IQ of 69 versus 71, yet one may be diagnosed with a disability and the other may not.

"We know a variety of factors contribute to IQ score, including genetics, as a child's IQ is highly correlated with that of his or her parents and siblings. Therefore, an important factor to take into consideration when interpreting IQ is family background," said Dr. Ledbetter. "Imagine if we have a child with a genetic abnormality, but the child's IQ is 85. Technically, we would not diagnose this child with a disability. However, if the family of this child has IQs around 130, we could consider that this child's genetic anomaly has 'cost' him or her 45 IQ points -- a very substantial difference."

According to Dr. Myers, "One implication of this concept is that studies designed to investigate the causes and mechanisms of developmental brain dysfunction should focus on measurement of quantifiable neuropsychological and neurobehavioral traits across groups of individuals with different clinical diagnoses. Another is that whenever possible, individuals with a particular genetic variant or other risk factor should be compared to their unaffected family members, not just to population norms."

Other authors on the paper were Thomas Challman, M.D. of Geisinger; Daniel Moreno De Luca, M.D., of Yale University, New Haven, Conn.; and David Evans, Ph.D., of Bucknell University, Lewisburg, Pa.

Andres Moreno-De-Luca, Scott M Myers, Thomas D Challman, Daniel Moreno-De-Luca, David W Evans, David H Ledbetter. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. The Lancet Neurology, 2013; 12 (4): 406 DOI: 10.1016/S1474-4422(13)70011-5

<http://www.sciencedaily.com/releases/2013/04/130402182457.htm>

Feeling Hungry May Protect the Brain Against Alzheimer's Disease

The feeling of hunger itself may protect against Alzheimer's disease.

The feeling of hunger itself may protect against Alzheimer's disease, according to study published today in the journal PLOS ONE. Interestingly, the results of this study in mice suggest that mild hunger pangs, and related hormonal pathways, may be as important to the much-discussed value of "caloric restriction" as actually eating less.

Caloric restriction is a regimen where an individual consumes fewer calories than average, but not so few that they become malnourished. Studies in many species have suggested that it could protect against neurodegenerative disorders and extend lifespans, but the effect has not been confirmed in human randomized clinical trials. Efforts to understand how cutting calories may protect the brain have grown increasingly important with news that American Alzheimer's deaths are increasing, and because the best available treatments only delay onset in a subset of patients.

Study authors argue that hormonal signals are the middlemen between an empty gut and the perception of hunger in the brain, and that manipulating them may effectively counter age-related cognitive decline in the same way as caloric restriction.

"This is the first paper, as far as we are aware, to show that the sensation of hunger can reduce Alzheimer's disease pathology in a mouse model of the disease," said Inga Kadish, Ph.D., assistant professor in the Department of Cell, Developmental and Integrative Biology (CDIB) within the School of Medicine at the University of Alabama at Birmingham. "If the mechanisms are confirmed, hormonal hunger signaling may represent a new way to combat Alzheimer's disease, either by itself or combined with caloric restriction." The team theorizes that feeling hungry creates mild stress. That, in turn, fires up metabolic signaling pathways that counter plaque deposits known to destroy nerve cells in Alzheimer's patients. The idea is an example of hormesis theory, where damaging stressors like starvation are thought to be good for you when experienced to a lesser degree.

To study the sensation of hunger, the research team analyzed the effects of the hormone ghrelin, which is known to make us feel hungry. They used a synthetic form of ghrelin in pill form, which let them control dosage such that the ghrelin-treated mice felt steadily, mildly hungry.

If it could be developed, a treatment that affected biochemical pathways downstream of hunger signals might help delay cognitive decline without consigning people to a life of feeling hungry. Straight caloric restriction would not be tolerable for many persons over the long-run, but manipulating post-hunger signaling might.

This line of thinking becomes important because any protective benefit brought about by drugs or diets that mildly adjust post-hunger signals might be most useful if started in those at risk as early in life as possible.

Attempts to treat the disease years later -- when nerve networks are damaged enough for neurological symptoms to appear -- may be too late. In the current study, it was long-term treatment with a ghrelin agonist that improved cognitive performance in mice tested when they had reached an advanced age.

Study details The study looked at whether or not the feeling of hunger, in the absence of caloric restriction, could counter Alzheimer's pathology in mice genetically engineered to have three genetic mutations known to cause the disease in humans.

Study mice were divided into three groups: one that received the 'synthetic ghrelin' (ghrelin agonist), a second that underwent caloric restriction (20 percent less food) and a third group that was fed normally. Study measures looked at each group's ability to remember, their degree of Alzheimer's pathology and their level of related, potentially harmful immune cell activation.

Results of such studies are most appropriately presented in terms of general trends in the data and statistical assessments of their likelihood if only chance factors were in play, a trait captured in each result's P value (the smaller the better). Thus, the first formal result of the study are that, in mice with the human Alzheimer's mutations, both the group treated with the ghrelin agonist LY444711 and the group that underwent caloric restriction performed significantly better in the water maze than did than mice fed normally ($p=0.023$).

The water maze is the standard test used to measure mouse memory. Researchers put mice in a pool with an invisible platform on which they could rest, and measured how quickly the mice found the platform in a series of tests. Mice with normal memory will remember where the platform is, and find it more quickly each time they are placed in the pool. Ghrelin agonist-treated mice found the hidden platform 26 percent faster than control mice, with caloric restricted mice doing so 23 percent faster than control mice.

The second result was a measure of the buildup of a cholesterol-related protein called amyloid beta in the forebrain, an early step in the destruction of nerve cells that accompanies Alzheimer's disease. The formal amyloid beta results show that mice either treated with the ghrelin agonist or calorically restricted had significantly less buildup of amyloid beta in the dentate gyrus, the part of the brain that controls memory function, than mice fed normally (i.e., control, 3.95 ± 0.83 ; LY, 2.05 ± 0.26 and CR, $1.28\pm 0.17\%$, respectively; Wilcoxon $p=0.04$).

The above results translate roughly into a 67 percent reduction of this pathology in caloric-restricted mice as compared to control mice, and a 48 percent reduction of amyloid beta deposits when comparing the ghrelin-treated mice with the control group. These percentages are neither final nor translatable to humans, but are simply meant to convey the idea of "better."

Finally, the team examined the difference in immune responses related to Alzheimer's pathology in each of the three groups. Microglia are the immune cells of the brain, engulfing and removing invading pathogens and dead tissue. They have also been implicated in several diseases when their misplaced activation damages tissues. The team found that mice receiving the ghrelin agonist treatment had both reduced levels of microglial activation compared to the control group, similar to the effect of caloric restriction.

The ghrelin agonist used in the study does not lend itself to clinical use and will not play a role in the future prevention of Alzheimer's disease, said Kadish. It was meant instead to prove a principle that hormonal hunger signaling itself can counter Alzheimer's pathology in a mammal. The next step is to understand exactly how it achieved this as a prerequisite to future treatment design.

Ghrelin is known to create hunger signals by interacting with the arcuate nucleus in the part of the brain called the hypothalamus, which then sends out signaling neuropeptides that help the body sense and respond to energy needs. Studies already underway in Kadish's lab seek to determine the potential role of these pathways and related genes in countering disease.

"Our group in the School of Public Health was studying whether or not a ghrelin agonist could make mice hungry as we sought to unravel mechanisms contributing to the life-prolonging effects of caloric restriction," said David Allison, Ph.D., associate dean for Science in the UAB School of Public Health and the project's initiator.

"Because of the interdisciplinary nature of UAB, our work with Dr. Allison led to an amazing conversation with Dr. Kadish about how we might combine our research with her longtime expertise in neurology because caloric restriction had been shown in early studies to counter Alzheimer's disease," said Emily Dhurandhar, Ph.D., a trainee in the UAB Nutrition Obesity Research Center and first study author. "The current study is the result."

About the research team Along with Kadish, Allison, and Dhurandhar, Thomas van Groen, Ph.D., associate professor in UAB's CDIB co-authored the paper.

Eli Lilly donated of the ghrelin agonist used in the study. This work was also supported by Alzheimer's of Central Alabama, the National Institutes of Health Obesity Training Grant (T32DK062710), and the National Institutes of Health Behavioral Assessment Core of UAB (P30 NS47466). Allison disclosed consulting relationships with industry, the details of which are included in the PLOS ONE article.

Emily J. Dhurandhar, David B. Allison, Thomas van Groen, Inga Kadish. Hunger in the Absence of Caloric Restriction Improves Cognition and Attenuates Alzheimer's Disease Pathology in a Mouse Model. PLoS ONE, 2013; 8 (4): e60437 DOI: 10.1371/journal.pone.0060437

<http://www.sciencedaily.com/releases/2013/04/130403072003.htm>

Immune System: The Healing Element Is Also the Enemy

The same factor in our immune system that is instrumental in enabling us to fight off severe and dangerous inflammatory ailments is also a player in doing the opposite at a later stage, causing the suppression of our immune response.

Why and how this happens and what can be done to mediate this process for the benefit of humankind is the subject of an article published online in the journal *Immunity* by Ph.D. student Moshe Sade-Feldman and Prof. Michal Baniyash of the Lautenberg Center for General and Tumor Immunology at the Institute for Medical Research Israel-Canada at the Hebrew University Faculty of Medicine.

Chronic inflammation poses a major global health problem and is common to different pathologies -- such as autoimmune diseases (diabetes, rheumatoid arthritis, lupus and Crohn's), chronic inflammatory disorders, chronic infections (HIV, leprosy, leishmaniasis) and cancer. Cumulative data indicate that at a certain stage of each of these diseases, the immune system becomes suppressed and results in disease progression.

In their previous work, the Hebrew University researchers had shown that in the course of chronic inflammation, unique immune system cells with suppressive features termed myeloid derived suppressor cells (MDSCs) are generated in the bone marrow and migrate into the body's organs and blood, imposing a general immune suppression.

A complex network of inflammatory compounds persistently secreted by the body's normal or cancerous cells support MDSC accumulation, activation and suppressive functions. One of these compounds is tumor necrosis factor- α (TNF- α), which under acute immune responses (short episodes), displays beneficial effects in the initiation of immune responses directed against invading pathogens and tumor cells.

However, TNF- α also displays harmful features under chronic responses, as described in pathologies such as rheumatoid arthritis, psoriasis, type II diabetes, Crohn's disease and cancer, leading to complications and disease progression. Therefore, today several FDA- approved TNF- α blocking reagents are used in the clinic for the treatment of such pathologies.

What has remained unclear until now, however, is just how TNF- α plays its deleterious role in manipulating the host's immune system towards the generation of a suppressive environment.

In their work, the Hebrew University researchers discovered the mechanisms underlying the TNF- α function, a key to controlling this factor and manipulating it, perhaps, for the benefit of humans. Using experimental mouse models, they showed unequivocally how TNF- α is critical in the induction of immune suppression generated

during chronic inflammation. The TNF-a was seen to directly affect the accumulation and suppressive function of MDSCs, leading to an impaired host's immune responses as reflected by the inability to respond against invading pathogens or against developing tumors.

Further, the direct role of how TNF-a works in humans was mimicked by injecting the FDA-approved anti-TNF-a drug, etanercept, into mice at the exacerbated stage of an inflammatory response, when MDSC accumulation was observed in the blood. The etanercept treatment changed the features of MDSCs and abolished their suppressive activity, leading to the restoration of the host's immune function.

Taken together, the results show clearly how the TNF-a-mediated inflammatory response, whether acute or chronic, will dictate its beneficial or harmful consequence on the immune system. While during acute inflammation TNF-a is vital for immediate immune defense against pathogens and clearance of tumor cells, during chronic inflammation -- under conditions where the host is unable to clear the pathogen or the tumor cells -- TNF-a is harmful due to the induction of immune suppression.

These results, providing new insight into the relationship between TNF-a and the development of an immune suppression during chronic inflammation, may aid in the generation of better therapeutic strategies against various pathologies when elevated TNF-a and MDSC levels are detected, as seen, for example, in tumor growths.

Moshe Sade-Feldman, Julia Kanterman, Eliran Ish-Shalom, Mazal Elnekave, Elad Horwitz, Michal Baniyash. Tumor Necrosis Factor- α Blocks Differentiation and Enhances Suppressive Activity of Immature Myeloid Cells during Chronic Inflammation. Immunity, 2013; 38 (3): 541 DOI: 10.1016/j.immuni.2013.02.007

http://www.eurekalert.org/pub_releases/2013-04/miot-sfi040313.php

Study finds ionic thrusters generate efficient propulsion in air

Thrusters powered by ionic wind may be an efficient alternative to conventional atmospheric propulsion technologies

Written by Jennifer Chu, MIT News Office

CAMBRIDGE, MA -- When a current passes between two electrodes — one thinner than the other — it creates a wind in the air between. If enough voltage is applied, the resulting wind can produce a thrust without the help of motors or fuel.

This phenomenon, called electrohydrodynamic thrust — or, more colloquially, "ionic wind" — was first identified in the 1960s. Since then, ionic wind has largely been limited to science-fair projects and basement experiments; hobbyists have posted hundreds of how-to videos on building "ionocrafts" — lightweight vehicles made of balsa wood, aluminum foil and wire — that lift off and hover with increased voltage.

Despite this wealth of hobbyist information, there have been few rigorous studies of ionic wind as a viable propulsion system. Some researchers have theorized that ionic thrusters, if used as jet propulsion, would be extremely inefficient, requiring massive amounts of electricity to produce enough thrust to propel a vehicle. Now researchers at MIT have run their own experiments and found that ionic thrusters may be a far more efficient source of propulsion than conventional jet engines. In their experiments, they found that ionic wind produces 110 newtons of thrust per kilowatt, compared with a jet engine's 2 newtons per kilowatt. The team has published its results in the Proceedings of the Royal Society.

Steven Barrett, an assistant professor of aeronautics and astronautics at MIT, envisions that ionic wind may be used as a propulsion system for small, lightweight aircraft. In addition to their relatively high efficiency, ionic thrusters are silent, and invisible in infrared, as they give off no heat — ideal traits, he says, for a surveillance vehicle.

"You could imagine all sorts of military or security benefits to having a silent propulsion system with no infrared signature," says Barrett, who co-authored the paper with graduate student Kento Masuyama.

Shooting the gap

A basic ionic thruster consists of three parts: a very thin copper electrode, called an emitter; a thicker tube of aluminum, known as a collector; and the air gap in between. A lightweight frame typically supports the wires, which connect to an electrical power source. As voltage is applied, the field gradient strips away electrons from nearby air molecules. These newly ionized molecules are strongly repelled by the corona wire, and strongly attracted to the collector. As this cloud of ions moves toward the collector, it collides with surrounding neutral air molecules, pushing them along and creating a wind, or thrust.

To measure an ion thruster's efficiency, Barrett and Masuyama built a similarly simple setup, and hung the contraption under a suspended digital scale. They applied tens of thousands of volts, creating enough current draw to power an incandescent light bulb. They altered the distance between the electrodes, and recorded the thrust as the device lifted off the ground. Barrett says that the device was most efficient at producing lower thrust — a desirable, albeit counterintuitive, result.

"It's kind of surprising, but if you have a high-velocity jet, you leave in your wake a load of wasted kinetic energy," Barrett explains. "So you want as low-velocity a jet as you can, while still producing enough thrust." He adds that an ionic wind is a good way to produce a low-velocity jet over a large area.

Getting to liftoff

Barrett acknowledges that there is one big obstacle to ionic wind propulsion: thrust density, or the amount of thrust produced per given area. Ionic thrusters depend on the wind produced between electrodes; the larger the space between electrodes, the stronger the thrust produced. That means lifting a small aircraft and its electrical power supply would require a very large air gap. Barrett envisions that electrodynamic thrusters for aircraft — if they worked — would encompass the entire vehicle.

Another drawback is the voltage needed to get a vehicle off the ground: Small, lightweight balsa models require several kilovolts. Barrett estimates a small craft, with onboard instrumentation and a power supply, would need hundreds or thousands of kilovolts.

"The voltages could get enormous," Barrett says. "But I think that's a challenge that's probably solvable." For example, he says power might be supplied by lightweight solar panels or fuel cells. Barrett says ionic thrusters might also prove useful in quieter cooling systems for laptops.

"Efficiency is probably the number one thing overall that drives aircraft design," Barrett says. "[Ionic thrusters] are viable insofar as they are efficient. There are still unanswered questions, but because they seem so efficient, it's definitely worth investigating further."

http://www.eurekalert.org/pub_releases/2013-04/sri-sif040313.php

Scientists identify first potentially effective therapy for human prion disease

For the first time scientists identify a pair of drugs already approved for human use that show anti-prion activity

JUPITER, FL - Human diseases caused by misfolded proteins known as prions are some of most rare yet terrifying on the planet—incurable with disturbing symptoms that include dementia, personality shifts, hallucinations and coordination problems. The most well-known of these is Creutzfeldt-Jakob disease, which can be described as the naturally occurring human equivalent of mad cow disease.

Now, scientists from the Florida campus of The Scripps Research Institute (TSRI) have for the first time identified a pair of drugs already approved for human use that show anti-prion activity and, for one of them, great promise in treating these universally fatal disorders.

The study, led by TSRI Professor Corinne Lasmézas and performed in collaboration with TSRI Professor Emeritus Charles Weissmann and Director of Lead Identification Peter Hodder, was published this week online ahead of print by the journal *Proceedings of the National Academy of Sciences*.

The new study used an innovative high-throughput screening technique to uncover compounds that decrease the amount of the normal form of the prion protein (PrP, which becomes distorted by the disease) at the cell surface. The scientists found two compounds that reduced PrP on cell surfaces by approximately 70 percent in the screening and follow up tests. The two compounds are already marketed as the drugs tacrolimus and astemizole. Tacrolimus is an immune suppressant widely used in organ transplantation. Tacrolimus could prove problematic as an anti-prion drug, however, because of issues including possible neurotoxicity.

However, astemizole is an antihistamine that has potential for use as an anti-prion drug. While withdrawn voluntarily from the U.S. over-the-counter market in 1999 because of rare cardiac arrhythmias when used in high doses, it has been available in generic form in more than 30 countries and has a well-established safety profile. Astemizole not only crosses the blood-brain barrier, but works effectively at a relatively low concentration.

Lasmézas noted that astemizole appears to stimulate autophagy, the process by which cells eliminate unwanted components. "Autophagy is involved in several protein misfolding neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases," she said. "So future studies on the mode of action of astemizole may uncover potentially new therapeutic targets for prion diseases and similar disorders."

The study noted that eliminating cell surface PrP expression could also be a potentially new approach to treat Alzheimer's disease, which is characterized by the build-up of amyloid β plaque in the brain. PrP is a cell surface receptor for A β peptides and helps mediate a number of critical deleterious processes in animal models of the disease.

The first author of the study, "Unique Drug Screening Approach for Prion Diseases Identifies Tacrolimus and Astemizole as Antiprion Agents," is Yervand Eduard Karapetyan of The Scripps Research Institute. Other authors include Gian Franco Sferrazza, Minghai Zhou, Gregory Ottenberg, Timothy Spicer, Peter Chase, Mohammad Fallahi, Peter Hodder and Charles Weissmann of The Scripps Research Institute. For more information on the study, see <http://www.pnas.org/content/early/2013/03/29/1303510110.abstract>

The research was supported by The Scripps Research Institute, the Alafi Foundation and the National Institutes of Health (Grant MH084512).

http://www.eurekalert.org/pub_releases/2013-04/bmj-bl040213.php

Baldness linked to increased risk of coronary heart disease

Risk greatest for those with thinning crown rather than receding hairline

Male pattern baldness is linked to an increased risk of coronary heart disease, but only if it's on the top/crown of the head, rather than at the front, finds an analysis of published evidence in the online journal BMJ Open.

A receding hairline is not linked to an increased risk, the analysis indicates.

The researchers trawled the Medline and the Cochrane Library databases for research published on male pattern baldness and coronary heart disease, and came up with 850 possible studies, published between 1950 and 2012.

But only six satisfied all the eligibility criteria and so were included in the analysis. All had been published between 1993 and 2008, and involved just under 40,000 men. Three of the studies were cohort studies - meaning that the health of balding men was tracked for at least 11 years.

Analysis of the findings from these showed that men who had lost most of their hair were a third more likely (32%) to develop coronary artery disease than their peers who retained a full head of hair.

When the analysis was confined to men under the age of 55-60, a similar pattern emerged. Bald or extensively balding men were 44% more likely to develop coronary artery disease.

Analysis of the other three studies, which compared the heart health of those who were bald / balding with those who were not, painted a similar picture. It showed that balding men were 70% more likely to have heart disease, and those in younger age groups were 84% more likely to do so.

Three studies assessed the degree of baldness using a validated scale (Hamilton scale). Analysis of these results indicated that the risk of coronary artery disease depended on baldness severity, but only if this was on the top/crown of the head, known as the vertex.

Extensive vertex baldness boosted the risk by 48%, moderate vertex baldness by 36%, and mild vertex baldness by 18%. By contrast, a receding hairline made very little difference to risk, the analysis showed.

To compensate for differences in the methods of assessing baldness in the studies included in the analysis, the authors looked at four differing grades of baldness: none; frontal; crown-top; combined.

Once again, this indicated that the severity of baldness affected the risk of coronary heart disease.

Men with both frontal and crown-top baldness were 69% more likely to have coronary artery disease than those with a full head of hair, while those with just crown-top baldness were 52% more likely to do so. Those with just frontal baldness were 22% more likely to do so.

Explanations for the reasons behind the association vary, but include the possibility that baldness may indicate insulin resistance, a precursor to diabetes; a state of chronic inflammation; or increased sensitivity to testosterone, all of which are involved directly or indirectly in promoting cardiovascular disease, say the authors.

But they conclude: "[Our] findings suggest that vertex baldness is more closely associated with systemic atherosclerosis than with frontal baldness. Thus, cardiovascular risk factors should be reviewed carefully in men with vertex baldness, especially younger men" who should "probably be encouraged to improve their cardiovascular risk profile."

[Male pattern baldness and its association with coronary heart disease: a meta-analysis doi 10.1136/bmjopen-2012-002537]

http://www.eurekalert.org/pub_releases/2013-04/ez-af040213.php

A fingerprint of exhaled breath

Modern high-resolution analytical methods that can provide real-time information on the chemical composition of exhaled breath

Bodily fluids contain lots of information about the health status of a person. Medical doctors routinely have blood and urine analysed in order to obtain hints for infectious and metabolic diseases, to diagnose cancer and organ failure, and to check the dose of medication, based on compounds present in these body fluids.

Researchers at ETH Zurich and at the University Hospital Zurich now propose to extend such analyses to breath, and in particular to take advantage of modern high-resolution analytical methods that can provide real-time information on the chemical composition of exhaled breath.

Unbiased Chemical Analysis of Breath

The scientists developed an instrument-based version of a principle that has been known for a long time in traditional Chinese medicine: TCM doctors draw conclusions about the health state of a patient based on the smell of the exhaled breath. It is also known that trained dogs and rats can distinguish the smell of the breath of people suffering from certain variants of cancer. In these cases the entire smell of the patient's exhaled breath is gauged, which can give rise to bias. The scientists, led by Renato Zenobi, professor at the Laboratory for

Organic Chemistry, aim at eliminating this bias and identifying the chemical compounds in breath. Like this, doctors should be able to use specific compounds, which are present in breath at minute concentrations, for medical diagnosis.

Using mass spectrometry, these goals can be reached, as shown in a recent study where the ETH researchers analysed the exhaled breath of eleven volunteers. They found that the chemical "fingerprint" of exhaled breath, largely based on volatile and semi-volatile metabolites, shows an individual core pattern. Each volunteer was found to have his/her own characteristic "breathprint".

Stable Pattern

Using regular measurements extending over 11 days, the researchers could furthermore show that this metabolic "breathprint" stays constant. "We did find some small variations during the day, but overall the individual pattern stays sufficiently constant to be useful for medical purposes", says Pablo Martinez-Lozano Sinues, senior scientist in Zenobi's research group. If the measurements would show too large variations, they would not be useful for medical diagnosis.

To carry out these measurements, Zenobi and his colleagues modified commercial mass spectrometers, for example by adding a breath sampling inlet line that delivers exhaled breath from a mouth piece directly into the ion source of the instrument. Mass spectra showing peaks of roughly 100 compounds in breath can be easily and rapidly obtained in this fashion. The researchers were able to identify acetone, a product of the sugar metabolism. Most of the other signals present in the "breathprints" have not been assigned yet, which is something the scientists have on their to-do-list.

Chemical fingerprints of diseases

The next step the ETH chemists plan to take is not only to elucidate the personal breathprints of individuals, but to recognize characteristic patterns of diseases with the same technology. For this endeavour, they are collaborating with medical doctors at the Division of Pulmonology of the University Hospital Zurich. "If we find a consistent pattern in patients with a given lung disease, we can develop a diagnostic tool", explains Sinues. They believe that their chances are highest to find characteristic biomarkers in the exhaled breath of patients with lung diseases, which is why they focus on these disorders. In the future, they hope to extend their methodology to other groups of diseases.

Although the potential usefulness of analysing breath for medical diagnosis has been known, it is rarely done in academic medicine. "This might be due to the fact that existing methods for breath analysis are either rather slow, or are limited to a small number of compounds that they can detect", says Sinues.

Compared to analysis of blood or urine, a significant advantage of the approach the ETH researchers have taken is that the breath fingerprint is available within seconds after delivering the breath sample. Analysing urine or blood in a specialized laboratory usually takes a lot longer. Another advantage is that exhaling into the ion source of a mass spectrometer is completely non-invasive, i.e., there is no need to poke the patient with a needle (when a blood sample is taken). "Our goal is to develop breath analysis to the point where it becomes competitive with the established analysis of blood and urine", says Malcolm Kohler, professor at the University Hospital Zurich, and one of the co-authors of the study. Regular survey of breath could, for example, be used to obtain an early warning for healthy persons with a known risk for a certain disease. It is also imaginable to monitor the progress or the side effects of an on-going medical therapy.

For this method to be accepted in the clinic, the instrumentation has to be improved. The highly sensitive and accurate mass spectrometers that are currently used for these analyses are large and expensive. Zenobi: "Small, portable mass spectrometers already exist; if their performance can be improved, they will eventually find their way into clinics and doctor's offices."

http://www.eurekalert.org/pub_releases/2013-04/sumc-aoc040113.php

Accused of complicity in Alzheimer's, amyloid proteins may be getting a bad rap

Amyloids - clumps of misfolded proteins found in the brains of people with Alzheimer's disease and other neurodegenerative disorders - are the quintessential bad boys of neurobiology.

STANFORD, Calif. They're thought to muck up the seamless workings of the neurons responsible for memory and movement, and researchers around the world have devoted themselves to devising ways of blocking their production or accumulation in humans. But now a pair of recent research studies from the Stanford University School of Medicine sets a solid course toward rehabilitating the reputation of the proteins that form these amyloid tangles, or plaques. In the process, they appear poised to turn the field of neurobiology on its head. The first study, published in August, showed that an amyloid-forming protein called beta amyloid, which is strongly implicated in Alzheimer's disease, could reverse the symptoms of a multiple-sclerosis-like neurodegenerative disease in laboratory mice.

The second study, to be published April 3 in *Science Translational Medicine*, extends the finding to show that small portions of several notorious amyloid-forming proteins (including well-known culprits like tau and prion proteins) can also quickly alleviate symptoms in mice with the condition — despite the fact that the fragments can and do form the long tendrils, or fibrils, previously thought harmful to nerve health.

"What we're finding is that, at least under certain circumstances, these amyloid peptides actually help the brain," said Lawrence Steinman, MD, professor of neurology and neurological sciences and of pediatrics. "This really turns the 'amyloid-is-bad' dogma upside down. It will require a shift in people's fundamental beliefs about neurodegeneration and diseases like multiple sclerosis, Alzheimer's and Parkinson's."

Steinman is a noted expert in multiple sclerosis whose research led to the development of natalizumab (marketed as Tysabri), a potent treatment for the disease.

Taken together, the studies begin to suggest the radical new idea that full-length, amyloid-forming proteins may in fact be produced by the body as a protective, rather than destructive, force. In particular, Steinman's study shows that these proteins may function as molecular chaperones, escorting and removing from sites of injury specific molecules involved in inflammation and inappropriate immune responses.

Steinman, who is also the medical school's George A. Zimmermann Professor, is the corresponding author of the research. Jonathan Rothbard, PhD, a senior research scientist in the Steinman laboratory, is the senior author; postdoctoral scholar Michael Kurnellas, PhD, is the lead author.

Although the specific findings of Steinman's two studies are surprising, there have been inklings from previous research that amyloid-forming proteins may not be all bad. In particular, inhibiting, or knocking out, the expression of several of the proteins in the mouse models of multiple sclerosis — a technique that should block the course of the disease if these proteins are the cause — instead worsened the animals' symptoms.

And there's the fact that these so-called dangerous amyloid-forming molecules are surprisingly prevalent. "We know the body makes a lot of amyloid-forming proteins in response to injury," said Steinman. "I'm doubtful that that's done to produce more harm. For example, the prion protein is found in every cell in our bodies. What is it doing? It's possible that any therapeutic maneuver to remove all of these proteins could interfere with their natural function."

Understanding how amyloids form requires an understanding of the biology of proteins, which are essentially strings of smaller components called amino acids attached end to end. Once they're made, these protein strings twist and fold into specific three-dimensional shapes that fit together like keys and locks to do the work of the cell.

A misfolded protein is likely to be unable to carry out its duties and must be disposed of by the body's cellular waste-management system. Amyloid-forming proteins (of which there are around 20), however, don't go quietly, if at all. Instead, they initiate a chain reaction with other misfolded proteins — forming long, insoluble strands called fibrils that mat together to form amyloid clumps. These clumps appear consistently in the brains of people with neurodegenerative diseases like Alzheimer's and multiple sclerosis, but not in the brains of healthy people.

Although these clumps are thought to be detrimental to nerve cells, it's not entirely clear how they cause harm. One possibility is the ability of the fibrils to form cylindrical pores that could disrupt the cellular membrane and interfere with the orderly flow of ions and molecules used by the cells to communicate and transmit nerve signals. Regardless, their very presence suggests a diagnosis of neurodegeneration to many clinicians, including — until recently — Steinman.

"We began this research because these molecules are present in the brains of people with multiple sclerosis," said Steinman. "We expected to show that the presence of beta amyloid made the disease worse in laboratory animals. Instead, we saw a great deal of benefit."

Intrigued by the results of their first study, the researchers next tested the effect of small, six-amino-acid portions of several amyloid-forming proteins, including beta amyloid, which appeared likely to share a three-dimensional structure. They found that nearly all of the tiny protein molecules, or hexamers, were also able to temporarily reverse the symptoms of multiple sclerosis in the mice (when the treatment was stopped, the mice developed signs of the condition within a few days).

The researchers noted, however, that the curative effect of the hexamers was linked to their ability to form fibrils similar, but not identical, to their longer parent molecules. For example, these simplified hexamer fibrils are more easily formed and broken apart than those composed of whole proteins. They are also thought not to be able to form the cylindrical pores that might damage cell membranes. Finally, the hexamer fibrils appear to inhibit the formation of fibrils from full-length proteins — perhaps by blocking, or failing to promote, the chain reaction that initiates fibril formation.

When Steinman and his colleagues mixed the fibril-forming hexamers with blood plasma from three people with multiple sclerosis, they found that the fibrils bound to and removed from solution many potentially damaging molecules involved in inflammation and the immune response.

"These hexamer fibrils appear to be working to remove dangerous chemicals from the vicinity of the injury," said Steinman.

The researchers are eager to pursue the use of these small hexamers as therapies for neurodegenerative diseases like multiple sclerosis. Much research is still needed, but Steinman is hopeful.

"The lessons we learn from our study of amyloid-forming proteins in multiple sclerosis could be helpful for stroke and brain trauma, as well as for Alzheimer's," said Steinman. "We're gaining insight into how current therapeutic approaches may be affecting the body, and beginning to understand the nuances necessary to design a successful treatment. Although it will take time, we're determined to move promising results out of the laboratory and into the clinic as quickly as possible."

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Other Stanford authors of the study include staff scientist and director of proteomics Chris Adams, PhD, and professor of pathology Raymond Sobel, MD.

The research was supported by the National Multiple Sclerosis Society, the National Institutes of Health (grants NS55997, DK078123 and 1R43AI0949) and the Endriz Fund.

Information about Stanford's Department of Neurology and Neurological Sciences, which also supported the work, is available at <http://neurology.stanford.edu/>.

<http://www.sciencedaily.com/releases/2013/04/130403104104.htm>

Breakthrough in Hydrogen Fuel Production Could Revolutionize Alternative Energy Market

Researchers have discovered a way to extract large quantities of hydrogen from any plant

A team of Virginia Tech researchers has discovered a way to extract large quantities of hydrogen from any plant, a breakthrough that has the potential to bring a low-cost, environmentally friendly fuel source to the world.

"Our new process could help end our dependence on fossil fuels," said Y.H. Percival Zhang, an associate professor of biological systems engineering in the College of Agriculture and Life Sciences and the College of Engineering. "Hydrogen is one of the most important biofuels of the future."

Zhang and his team have succeeded in using xylose, the most abundant simple plant sugar, to produce a large quantity of hydrogen that previously was attainable only in theory. Zhang's method can be performed using any source of biomass.

The discovery is a featured editor's choice in an online version of the chemistry journal *Angewandte Chemie, International Edition*.

This new environmentally friendly method of producing hydrogen utilizes renewable natural resources, releases almost no greenhouse gases, and does not require costly or heavy metals. Previous methods to produce hydrogen are expensive and create greenhouse gases.

The U.S. Department of Energy says that hydrogen fuel has the potential to dramatically reduce reliance of fossil fuels and automobile manufacturers are aggressively trying to develop vehicles that run on hydrogen fuel cells. Unlike gas-powered engines that spew out pollutants, the only byproduct of hydrogen fuel is water.

Zhang's discovery opens the door to an inexpensive, renewable source of hydrogen.

Jonathan R. Mielenz, group leader of the bioscience and technology biosciences division at the Oak Ridge National Laboratory, who is familiar with Zhang's work but not affiliated with this project, said this discovery has the potential to have a major impact on alternative energy production.

"The key to this exciting development is that Zhang is using the second most prevalent sugar in plants to produce this hydrogen," he said. "This amounts to a significant additional benefit to hydrogen production and it reduces the overall cost of producing hydrogen from biomass."

Mielenz said Zhang's process could find its way to the marketplace as quickly as three years if the technology is available. Zhang said when it does become commercially available, it has the possibility of making an enormous impact. "The potential for profit and environmental benefits are why so many automobile, oil, and energy companies are working on hydrogen fuel cell vehicles as the transportation of the future," Zhang said.

"Many people believe we will enter the hydrogen economy soon, with a market capacity of at least \$1 trillion in the United States alone."

Obstacles to commercial production of hydrogen gas from biomass previously included the high cost of the processes used and the relatively low quantity of the end product.

But Zhang thinks he has found the answers to those problems. For seven years, Zhang's team has been focused on finding non-traditional ways to produce high-yield hydrogen at low cost, specifically researching enzyme combinations, discovering novel enzymes, and engineering enzymes with desirable properties.

The team liberates the high-purity hydrogen under mild reaction conditions at 122 degree Fahrenheit and normal atmospheric pressure. The biocatalysts used to release the hydrogen are a group of enzymes artificially isolated from different microorganisms that thrive at extreme temperatures, some of which could grow at around the boiling point of water.

The researchers chose to use xylose, which comprises as much as 30 percent of plant cell walls. Despite its abundance, the use of xylose for releasing hydrogen has been limited. The natural or engineered microorganisms that most scientists use in their experiments cannot produce hydrogen in high yield because these microorganisms grow and reproduce instead of splitting water molecules to yield pure hydrogen. To liberate the hydrogen, Virginia Tech scientists separated a number of enzymes from their native microorganisms to create a customized enzyme cocktail that does not occur in nature. The enzymes, when combined with xylose and a polyphosphate, liberate the unprecedentedly high volume of hydrogen from xylose, resulting in the production of about three times as much hydrogen as other hydrogen-producing microorganisms. The energy stored in xylose splits water molecules, yielding high-purity hydrogen that can be directly utilized by proton-exchange membrane fuel cells. Even more appealing, this reaction occurs at low temperatures, generating hydrogen energy that is greater than the chemical energy stored in xylose and the polyphosphate. This results in an energy efficiency of more than 100 percent -- a net energy gain. That means that low-temperature waste heat can be used to produce high-quality chemical energy hydrogen for the first time. Other processes that convert sugar into biofuels such as ethanol and butanol always have energy efficiencies of less than 100 percent, resulting in an energy penalty.

In his previous research, Zhang used enzymes to produce hydrogen from starch, but the reaction required a food source that made the process too costly for mass production.

The commercial market for hydrogen gas is now around \$100 billion for hydrogen produced from natural gas, which is expensive to manufacture and generates a large amount of the greenhouse gas carbon dioxide. Industry most often uses hydrogen to manufacture ammonia for fertilizers and to refine petrochemicals, but an inexpensive, plentiful green hydrogen source can rapidly change that market.

"It really doesn't make sense to use non-renewable natural resources to produce hydrogen," Zhang said. "We think this discovery is a game-changer in the world of alternative energy."

Support for the current research comes from the Department of Biological Systems Engineering at Virginia Tech. Additional resources were contributed by the Shell GameChanger Program, the Virginia Tech College of Agriculture and Life Sciences' Biodesign and Bioprocessing Research Center, and the U.S. Department of Energy BioEnergy Science Center, along with the Division of Chemical Sciences, Geosciences and Biosciences, Office of Basic Energy Sciences of the Department of Energy. The lead author of the article, Julia S. Martin Del Campo, who works in Zhang's lab, received her Ph.D. grant from the Mexican Council of Science and Technology.

Julia S. Martín del Campo, Joseph Rollin, Suwan Myung, You Chun, Sanjeev Chandrayan, Rodrigo Patiño, Michael WW Adams, Y.-H. Percival Zhang. High-Yield Production of Dihydrogen from Xylose by Using a Synthetic Enzyme Cascade in a Cell-Free System. Angewandte Chemie International Edition, 2013; DOI: 10.1002/anie.201300766

<http://www.sciencedaily.com/releases/2013/04/130403131354.htm>

Breakthrough Cancer-Killing Treatment Has No Side-Effects in Mice: New Chemistry May Cure Human

Medical researchers have developed a new form of radiation therapy that successfully put cancer into remission in mice.

Cancer painfully ends more than 500,000 lives in the United States each year, according to the Centers for Disease Control and Prevention. The scientific crusade against cancer recently achieved a victory under the leadership of University of Missouri Curators' Professor M. Frederick Hawthorne. Hawthorne's team has developed a new form of radiation therapy that successfully put cancer into remission in mice. This innovative treatment produced none of the harmful side-effects of conventional chemo and radiation cancer therapies. Clinical trials in humans could begin soon after Hawthorne secures funding.

"Since the 1930s, scientists have sought success with a cancer treatment known as boron neutron capture therapy (BNCT)," said Hawthorne, a recent winner of the National Medal of Science awarded by President Obama in the White House. "Our team at MU's International Institute of Nano and Molecular Medicine finally found the way to make BNCT work by taking advantage of a cancer cell's biology with nanochemistry." Cancer cells grow faster than normal cells and in the process absorb more materials than normal cells. Hawthorne's team took advantage of that fact by getting cancer cells to take in and store a boron chemical

designed by Hawthorne. When those boron-infused cancer cells were exposed to neutrons, a subatomic particle, the boron atom shattered and selectively tore apart the cancer cells, sparing neighboring healthy cells.

The physical properties of boron made Hawthorne's technique possible. A particular form of boron will split when it captures a neutron and release lithium, helium and energy. Like pool balls careening around a billiards table, the helium and lithium atoms penetrate the cancer cell and destroy it from the inside without harming the surrounding tissues.

"A wide variety of cancers can be attacked with our BNCT technique," Hawthorne said. "The technique worked excellently in mice. We are ready to move on to trials in larger animals, then people. However, before we can start treating humans, we will need to build suitable equipment and facilities. When it is built, MU will have the first radiation therapy of this kind in the world."

P. J. Kueffer, C. A. Maitz, A. A. Khan, S. A. Schuster, N. I. Shlyakhtina, S. S. Jalisatgi, J. D. Brockman, D. W. Nigg, M. F. Hawthorne. Boron neutron capture therapy demonstrated in mice bearing EMT6 tumors following selective delivery of boron by rationally designed liposomes. Proceedings of the National Academy of Sciences, 2013; DOI: 10.1073/pnas.1303437110

<http://phys.org/news/2013-04-astronomers-billion-earth-like-planets.html>

Astronomers anticipate 100 billion Earth-like planets

Researchers at The University of Auckland have proposed a new method for finding Earth-like planets and they anticipate that the number will be in the order of 100 billion.

Phys.org - The strategy uses a technique called gravitational microlensing, currently used by a Japan-New Zealand collaboration called MOA (Microlensing Observations in Astrophysics) at New Zealand's Mt John Observatory. Their work will appear in the Oxford University Press journal Monthly Notices of the Royal Astronomical Society.

Lead author Dr Phil Yock from the University of Auckland's Department of Physics explains that the work will require a combination of data from microlensing and the NASA Kepler space telescope.

"Kepler finds Earth-sized planets that are quite close to parent stars, and it estimates that there are 17 billion such planets in the Milky Way. These planets are generally hotter than Earth, although some could be of a similar temperature (and therefore habitable) if they're orbiting a cool star called a red dwarf."

"Our proposal is to measure the number of Earth-mass planets orbiting stars at distances typically twice the Sun-Earth distance. Our planets will therefore be cooler than the Earth. By interpolating between the Kepler and MOA results, we should get a good estimate of the number of Earth-like, habitable planets in the Galaxy. We anticipate a number in the order of 100 billion."

"Of course, it will be a long way from measuring this number to actually finding inhabited planets, but it will be a step along the way."

The first planet orbiting a Sun-like star was not found until 1995, despite strenuous efforts by astronomers. Dr Yock explains that this reflects the difficulty of detecting from a distance a tiny non-luminous object like Earth orbiting a bright object like the Sun. The planet is lost in the glare of the star, so indirect methods of detection must be used.

Whereas Kepler measures the loss of light from a star when a planet orbits between us and the star, microlensing measures the deflection of light from a distant star that passes through a planetary system en route to Earth – an effect predicted by Einstein in 1936.

In recent years, microlensing has been used to detect several planets as large as Neptune and Jupiter. Dr Yock and colleagues have proposed a new microlensing strategy for detecting the tiny deflection caused by an Earth-sized planet. Simulations carried out by Dr Yock and his colleagues – students and former students from The University of Auckland and France – showed that Earth-sized planets could be detected more easily if a worldwide network of moderate-sized, robotic telescopes was available to monitor them.

Coincidentally, just such a network of 1m and 2m telescopes is now being deployed by Las Cumbres Observatory Global Telescope Network (LCOGT) in collaboration with SUPA/St Andrews (Scottish Universities Physics Alliance), with three telescopes in Chile, three in South Africa, three in Australia, and one each in Hawaii and Texas.

This network is used to study microlensing events in conjunction with the Liverpool Telescope in the Canary Islands which is owned and operated by Liverpool John Moores University.

It is expected that the data from this suite of telescopes will be supplemented by measurements using the existing 1.8m MOA telescope at Mt John, the 1.3m Polish telescope in Chile known as OGLE, and the recently opened 1.3m Harlingen telescope in Tasmania.

More information: The new work will appear in Monthly Notices of the Royal Astronomical Society (Oxford University Press): dx.doi.org/10.1093/mnras/stt318

<http://bit.ly/ZH31RY>

Powder women's eggs for home storage

JUST add water and sperm – any romance should be provided separately. In future, women who want to safeguard their fertility may be able to store their eggs at home as a powder.

04 April 2013 by Andy Coghlan

To revive them for an attempt at having a baby, all they would need to do is empty the sachet, add water, fertilise with sperm and implant the embryo.

"You can keep the powder at room temperature forever – and just add water to bring it back to life," says Amir Arav of Core Dynamics in Ness Ziona, Israel, who developed the method. The technique was demonstrated with cow eggs last month at Cryo, a conference on cold-preservation techniques for eggs, sperm and embryos held in Berlin, Germany.

Arav claims that his company's process avoids the expense and complications of storage in liquid nitrogen. During such refrigeration, ice crystals can damage cellular membranes. To avoid this, Arav first soaks the cells in a solution containing substances that displace most of the water in the cells and which help to prevent cold damage to tissue. The protective ingredients include the sugar trehalose, which enables animals such as wood frogs and tardigrades to survive freezing or dehydration. Marinated in this cryoprotectant solution, the eggs are then converted into a glass-like solid state through a process called vitrification. This involves rapid freezing, so that any residual water has insufficient time to form ice crystals. "It takes a tenth of a second to reach -200 °C," says Arav.

Vitrification is used to process human eggs before storage in liquid nitrogen. Now Arav has added a final stage to freeze-dry and "powderise" the oocytes. Residual frozen water is converted directly into a gas by storing the vitrified cells at -55 °C for a day under low pressures, which allows the water to sublime away.

What remains is a powder that can potentially be stored indefinitely. "It must be under a vacuum, without air, oxygen, light, or anything that could damage the cells," says Arav.

Of the 30 cow eggs Arav prepared this way, 23 were confirmed to be viable using a staining test. Arav says the technique already works on red blood cells and on human mononuclear cells from umbilical cord blood (PLoS One, doi.org/d4326g).

"We need to know whether the oocytes can be fertilised after freeze-drying, whether they then form normal embryos, and if they do, the extent to which they implant in the womb and develop into healthy offspring," says Claus Andersen of the University Hospital of Copenhagen, Denmark. "Further, if the vision is for women to take their freeze-dried eggs home with them, will those eggs deteriorate over time or lose their reproductive potential?" he asks. "The freeze-drying needs to be shown to be as good as the conventional method of freezing under liquid nitrogen, and this could take some time."

<http://phys.org/news/2013-04-wild-mice-natural-lyme-borreliosis.html>

Wild mice have natural protection against Lyme borreliosis

Wild mice are the primary hosts for Borrelia, which are transmitted by ticks.

Like humans, mice can become infected with Borrelia. However, not all mice that come into contact with these bacteria contract the dreaded Lyme disease: Animals with a particular gene variant are immune to the bacteria, as scientists from the universities of Zurich and Lund demonstrate. Wild mice are the primary hosts for Borrelia, which are transmitted by ticks. Springtime spells tick-time. Lyme borreliosis is the most common tick-borne disease in Switzerland: around 10,000 people a year become infected with the pathogen. The actual hosts for Borrelia, however, are wild mice. Like in humans, the pathogen is also transmitted by ticks in mice.



Ticks suck blood. About the saliva of infected ticks, Borrelia get into the blood stream of mice. Credit: UZH

Interestingly, not all mice are equally susceptible to the bacterium and individual animals are immune to the pathogen. Scientists from the universities of Zurich and Lund headed by evolutionary biologist Barbara Tschirren reveal that the difference in vulnerability among the animals is genetic in origin.

Protective gene variant

Tschirren and colleagues examined wild mice for signs of a Borrelia infection in a large-scale field study. Borrelia afzelii – the scientific name for the bacteria – feed on mouse blood. The researchers discovered that mice with a particular variant of the antigen receptor TLR2 were around three times less susceptible to Borrelia. "The immune system of mice with this receptor variant recognizes the pathogen better and can trigger an immune response more quickly to destroy the Borrelia in time," says Tschirren. Infected mice exhibit similar

symptoms to humans – especially joint complaints. Consequently, in the wild infected mice probably do not survive for very long and weakened animals soon fall victim to foxes and birds of prey.

Arms race between mice and Borrelia

The protective gene variant is advantageous for its carriers and, according to the researchers, gradually becoming prevalent in the mouse population. Nonetheless, it is unlikely that all mice will one day be resistant to Borrelia. "The increasing resistance in the host is bound to lead to adaptations in Borrelia," predicts Tschirren.

"We can observe the evolutionary adaptation through the rearmament in mice and the pathogen."

People also have the antigen receptor TLR2, but not the resistant gene variant observed in mice. Whether the evolutionary arms race between mice and Borrelia will have repercussions for people remains to be seen.

According to Tschirren, the bacterium does not necessarily have to become more aggressive for humans.

Provided by University of Zurich

Tschirren, B. et al. Polymorphisms at the innate immune receptor TLR2 are associated with Borrelia infection in a wild rodent population. Proceedings of the Royal Society B, 20130364. April 3, 2013. doi: 10.1098/rspb.2013.0364

http://www.eurekalert.org/pub_releases/2013-04/ip-sol040413.php

Shift of language function to right hemisphere impedes post-stroke aphasia recovery

Findings published in Restorative Neurology and Neuroscience

Amsterdam, NL - In a study designed to differentiate why some stroke patients recover from aphasia and others do not, investigators have found that a compensatory reorganization of language function to right hemispheric brain regions bodes poorly for language recovery. Patients who recovered from aphasia showed a return to normal left-hemispheric language activation patterns. These results, which may open up new rehabilitation strategies, are available in the current issue of Restorative Neurology and Neuroscience.

"Overall, approximately 30% of patients with stroke suffer from various types of aphasia, with this deficit most common in stroke with left middle cerebral artery territory damage. Some of the affected patients recover to a certain degree in the months and years following the stroke. The recovery process is modulated by several known factors, but the degree of the contribution of brain areas unaffected by stroke to the recovery process is less clear," says lead investigator Jerzy P. Szaflarski, MD, PhD, of the Departments of Neurology at the University of Alabama and University of Cincinnati Academic Health Center.

For the study, 27 right-handed adults who suffered from a left middle cerebral artery infarction at least one year prior to study enrollment were recruited. After language testing, 9 subjects were considered to have normal language ability while 18 were considered aphasic. Patients underwent a battery of language tests as well as a semantic decision/tone decision cognitive task during functional MRI (fMRI) in order to map language function. MRI scans were used to determine stroke volume.

The authors found that linguistic performance was better in those who had stronger left-hemispheric fMRI signals while performance was worse in those who had stronger signal-shifts to the right hemisphere. As expected, they also found a negative association between the size of the stroke and performance on some linguistic tests. Right cerebellar activation was also linked to better post-stroke language ability.

The authors say that while a shift to the non-dominant right hemisphere can restore language function in children who have experienced left-hemispheric injury or stroke, for adults such a shift may impede recovery. For adults, it is the left hemisphere that is necessary for language function preservation and/or recovery.

http://www.eurekalert.org/pub_releases/2013-04/uovm-tea040413.php

The equine Adam lived fairly recently: Close relationships among modern stallions

In mammals, an individual's sex is determined by the chromosomes it inherits from its parents.

Two X chromosomes lead to a female, whereas one X and one Y lead to a male. Y chromosomes are only passed from fathers to sons, so each Y chromosome represents the male genealogy of the animal in question. In contrast, mitochondria are passed on by mothers to all their offspring. This means that an analysis of the genetic material or DNA of mitochondria can give information on the female ancestry. For the modern horse, it is well known that mitochondrial DNA is extremely diverse and this has been interpreted to mean that many ancestral female horses have passed their DNA on to modern horse breeds. Until recently, though, essentially no sequence diversity had been detected on the Y chromosome of the domestic horse. Not only does the lack of sequence markers on the Y chromosome make it impossible to trace male lineages with confidence, it also represents a scientific paradox. How can a species with so many female lines have so few male lines? The issue has now been addressed by Barbara Wallner and colleagues at the Institute of Animal Breeding and Genetics, University of Veterinary Medicine, Vienna (Vetmeduni Vienna).

Wallner initially selected seventeen horses from a range of European breeds. She pooled their DNAs and used modern sequencing technology to examine the level of diversity on a 200 kb portion of the Y chromosome she had previously sequenced. The Y chromosomes were found to be highly similar: only five positions turned out

to be variable. As Wallner says, "the results confirmed what we had previously suspected: that the Y chromosomes of modern breeds of horse show far less variability than those of other domestic animals." The five variable positions, or polymorphisms, were nevertheless sufficient to enable the researchers to derive a type of "family tree" for the various breeds of modern horse they investigated. An examination of over 600 stallions from 58 (largely European) breeds showed that the animals could be grouped into six basic lines or haplotypes. The ancestral haplotype is distributed across almost all breeds and geographical regions. A second haplotype also occurs at high frequencies across a broad range of breeds, although not in northern European breeds or in horses from the Iberian Peninsula. A third haplotype is present in almost all English Thoroughbreds and in many warm-blooded breeds. The final three haplotypes are only found in local northern European breeds: one in Icelandic horses, one in Norwegian Fjord horses and one in Shetland ponies.

The pedigree of horses is very tightly controlled, with studbooks in many cases going as far back as the 18th century. Combining the results of the genetic analysis with pedigree data enabled the scientists to trace the paternal roots of many of the current male lines. Wallner feels that, "the results were intriguing, for example in the way the distribution of one haplotype reflects the widespread movement of stallions from the Middle East to Central and Western Europe in the past 200 years. Another haplotype results from a mutation that occurred in the famous English Thoroughbred stallion 'Eclipse' or in his son or grandson. It is amazing to see how much influence this line has had on modern sport horses: almost all English Thoroughbreds and nearly half the modern sport horse breeds carry the Eclipse haplotype."

The Vetmeduni Vienna scientists have confirmed the low diversity of the horse Y chromosome, which contrasts sharply with range of mitochondrial DNA haplotypes observed in modern horses. The difference is presumably due to the strong variation in male reproductive success. Wild horses have a polygynous breeding pattern, while the intensive breeding practices in domestic horses mean that single stallions can effectively pass on their DNA to entire generations. The senior author on the paper, Gottfried Brem, comments that, "most modern breeds were established in the last two centuries, during which time the horse has undergone a transition from working and military use towards leisure and sports. This has largely been achieved through the use in breeding of a few selected males. The restricted genetic diversity of the modern horse Y chromosome is a reflection of what has survived the species' dynamic history."

The paper "Identification of genetic variation on the horse Y chromosome and the tracing of male founder lineages in modern breeds" by Barbara Wallner, Claus Vogl, Priyank Shukla, Joerg P Burgstaller, Thomas Druml and Gottfried Brem has just been published online in "PLOS ONE".

The original article in full text online (Open Access): <http://dx.plos.org/10.1371/journal.pone.0060015>

http://www.eurekalert.org/pub_releases/2013-04/uol-pbp040413.php

Power behind primordial soup discovered

Researchers at the University of Leeds may have solved a key puzzle about how objects from space could have kindled life on Earth.

While it is generally accepted that some important ingredients for life came from meteorites bombarding the early Earth, scientists have not been able to explain how that inanimate rock transformed into the building blocks of life. This new study shows how a chemical, similar to one now found in all living cells and vital for generating the energy that makes something alive, could have been created when meteorites containing phosphorus minerals landed in hot, acidic pools of liquids around volcanoes, which were likely to have been common across the early Earth.

"The mystery of how living organisms sprung out of lifeless rock has long puzzled scientists, but we think that the unusual phosphorus chemicals we found could be a precursor to the batteries that now power all life on Earth. But the fact that it developed simply, in conditions similar to the early Earth, suggests this could be the missing link between geology and biology," said Dr Terry Kee, from the University's School of Chemistry, who led the research.

All life on Earth is powered by a process called chemiosmosis, where the chemical adenosine triphosphate (ATP), the rechargeable chemical 'battery' for life, is both broken down and re-formed during respiration to release energy used to drive the reactions of life, or metabolism. The complex enzymes required for both the creation and break down of ATP are unlikely to have existed on the Earth during the period when life first developed. This led scientists to look for a more basic chemical with similar properties to ATP, but that does not require enzymes to transfer energy.

Phosphorus is the key element in ATP, and other fundamental building blocks of life like DNA, but the form it commonly takes on Earth, phosphorus (V), is largely insoluble in water and has a low chemical reactivity. The early Earth, however, was regularly bombarded by meteorites and interstellar dust rich in exotic minerals, including the far more reactive form of phosphorus, the iron-nickel-phosphorus mineral schreibersite.

The scientists simulated the impact of such a meteorite with the hot, volcanically-active, early Earth by placing samples of the Sikhote-Alin meteorite, an iron meteorite which fell in Siberia in 1947, in acid taken from the Hveradalur geothermal area in Iceland. The rock was left to react with the acidic fluid in test tubes incubated by the surrounding hot spring for four days, followed by a further 30 days at room temperature.

In their analysis of the resulting solution the scientists found the compound pyrophosphite, a molecular 'cousin' of pyrophosphate – the part of ATP responsible for energy transfer. The scientists believe this compound could have acted as an earlier form of ATP in what they have dubbed 'chemical life'.

"Chemical life would have been the intermediary step between inorganic rock and the very first living biological cell. You could think of chemical life as a machine – a robot, for example, is capable of moving and reacting to surroundings, but it is not alive. With the aid of these primitive batteries, chemicals became organised in such a way as to be capable of more complex behaviour and would have eventually developed into the living biological structures we see today," said Dr Terry Kee.

The team from NASA's Jet Propulsion Laboratory (JPL-Caltech) working on the Curiosity rover, which landed on Mars in August last year, has recently reported the presence of phosphorus on the Red Planet.

"If Curiosity has found phosphorus in one of the forms we produced in Iceland, this may indicate that conditions on Mars were at one point suitable for the development of life in much the same way we now believe it developed on Earth," added Dr Kee.

The team at Leeds are now working with colleagues at JPL-Caltech to understand how these early batteries and the 'chemical life' they became part of might have developed into biological life. As part of this work they will be using facilities in the University of Leeds' Faculty of Engineering, currently used to test new fuel cells, to build a 'geological fuel cell' using minerals and gases common on the early Earth. Researchers will apply different chemicals to its surface and monitor the reactions take place and the chemical products which develop. The team also hope to travel to Disko Island in Greenland which is home to the Earth's only naturally-occurring source of schreibersite, the mineral found in the Sikhote-Alin meteorite. Here, they hope to repeat their experiments and show that the same chemicals develop in an entirely Earth-originated setting.

The paper Hydrothermal modification of the Sikhote-Alin iron meteorite under low pH geothermal environments. A plausibly prebiotic route to activated phosphorus on the early Earth was published online by the journal Geochimica et Cosmochimica Acta on 15th March 2013.

The research was funded by the Engineering and Physical Sciences Research Council, Leverhulme Trust, Science and Technology Facilities Council and the UK Space Agency.

http://www.sciencenews.org/view/feature/id/349370/description/Dose_of_Reality

Dose of Reality

HPV is epidemic, which is odd since it is largely preventable

By [Nathan Seppa](#)

There are two vaccines that guard against human papillomavirus, and they are in rare company among medical inventions — the vaccines prevent cancer. Only the hepatitis B vaccine can make the same claim. Cancer-causing HPV can trigger abnormal cell growth on the cervix, and cervical cancer still kills up to 4,000 U.S. women each year. The virus is also implicated in cancers occurring in the anus and the throat. All told, according to a 2011 study, 29 percent of sexually active U.S. girls and women carry a potentially cancer-causing HPV infection.

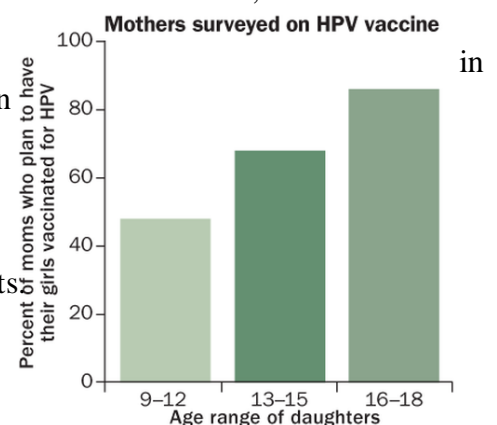
Back in 2006 and 2009, when the HPV vaccines Gardasil and Cervarix came onto the market, health officials dreamed of halting the spread of HPV, which is sexually transmitted, in a single generation. Scientists call such blanket coverage herd immunity — which a pathogen gets vaccinated into oblivion, becoming so rare that even unvaccinated people are protected.

With such heady potential, Gardasil, developed by Merck, and Cervarix, created by GlaxoSmithKline, should be an easy sell. They rev up a potent immunity against HPV 16 and 18, the two types of the virus that account for most cases of cervical cancer. Gardasil also prevents most genital warts.

The immunity the vaccines provide is many-fold better than the weak protection engendered by a run-in with the virus itself, and since approval, both vaccines have proven safe. A study of nearly 190,000 girls and women, published in 2012 in *Archives of Pediatric and Adolescent*

Medicine, found that the shots' most common side effects were mild skin infections and fainting.

Many U.S. mothers are reluctant to have preteen daughters vaccinated, even though that's when protection is most likely to prevent a future HPV infection. Source: J. Kahn et al/Pediatrics 2009



But the hope for herd immunity against HPV anytime soon is fading fast in most of the West. By 2011, only 53 percent of U.S. teenage girls from 13 to 17, a target group for the vaccines, had received them. “It’s a disaster,” says Andreas Kaufmann of Charité University Medicine Berlin, who sees the problem from the perspective of a biologist. “HPV is strictly species-specific. It only occurs in humans.” That means with mass vaccination, the virus would have no safe harbor in nature. “Theoretically, we could eradicate these HPV types, like we did smallpox,” he says. “We could end it.”

What’s the problem?

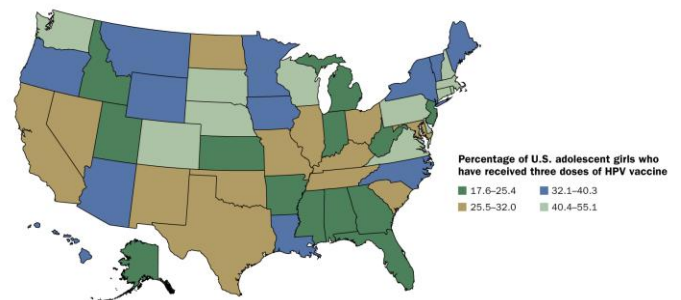
Most childhood immunizations are doled out in infancy. Although preteens and older kids routinely get shots or boosters for whooping cough, measles and meningitis, the HPV vaccines stand apart from those other shots like an unpopular kid.

For one thing, parents are uneasy about vaccinating a preteen against a virus associated with sexual activity. Researchers have found that some parents believe vaccination might lead to greater promiscuity. And a public scare about vaccines in general — including a false report linking the measles vaccine to autism — has contributed to the confusion. Not only that, but the vaccine is delivered in a three-shot regimen. Even among girls who get vaccinated, completing the course isn’t a certainty. Many U.S. preteen and teenage girls who start the course fail to get all three shots, and thus are less apt to be protected.

In the United States, responsibility for tracking kids’ HPV shots often falls to pediatricians, since the vaccine isn’t administered in schools. But pediatricians are notoriously overworked and — relative to many other physicians — underpaid. Doctors often need to cover vaccine costs up front to have them ready for patients, says Kevin Ault, a gynecologist at Emory University in Atlanta. Pediatricians also have to remind a patient to return for subsequent shots and often find themselves on the front line in contending with doubtful parents, says Noel Brewer, a health psychologist at the University of North Carolina in Chapel Hill. Instead of mass vaccinations in schools, the HPV vaccines depend on this hit-or-miss distribution system managed by individual doctors who, even if they advocate vaccination, may not want to cross parents. The result is often family indecision, procrastination and outright rejection.

Then there’s the behavior of the virus itself. The vaccines don’t work in people who have active HPV infections, and it’s difficult to know who those people are. The cancer-causing HPV types are stealthy, giving rise to phantom infections with no symptoms and an iffy risk of cancer far off in the future. These characteristics make the risks posed by HPV hard to grasp, says Christina Dorell, a physician at the Centers for Disease Control and Prevention. “With polio, people were getting sick and going to the hospital,” she says. “When the image of illness is removed from a group, you may have a little less sense of urgency coming from parents.”

Girls might see it differently, studies show. Doctors’ opinions matter to them. Those who receive a recommendation from a doctor are 2.6 times more likely to get vaccinated than girls getting no counsel, researchers reported in *Pediatrics* in 2011. Also, “there is no evidence of increased sexual-risk behavior, such as decreased condom use or earlier intercourse,” says Gregory Zimet, a clinical psychologist at the Indiana University School of Medicine in Indianapolis. Other work has found no increase in sexually transmitted diseases after HPV vaccination. “The whole [promiscuity] argument is false, actually,” Zimet says.



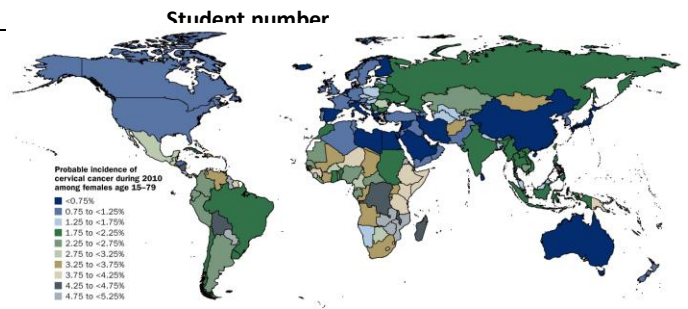
Health guidelines recommend the three-shot HPV vaccine for the best protection against cancer. But recipients don’t always complete the regimen. Compliance is worse in some states than in others. Source: A. Jemal et al/JNCI 2013;

Image: Geoatlas/Graphi-Ogre, adapted by E. Feliciano

More likely, many parents are in denial about their teens’ sexuality, says Kaufmann: “Parents don’t believe that a 15-year-old daughter may already be sexually active.” But a 2010 U.S. survey found that at least 12 percent of 14- and 15-year-old girls had engaged in oral sex or intercourse or both.

One way to skirt the problem might be to vaccinate earlier. Health psychologist Jo Waller of University College London says focus groups show that parents like the idea of vaccinating girls as young as age 8 or 9, since that means skipping the chat about how the vaccine prevents sexual transmission of HPV. “They wouldn’t have to open that can of worms,” she says. Some countries do begin vaccinating at age 9, and several trials are under way testing the effectiveness of the shots at that age.

The fact of the matter is that the science underlying the HPV link to cancer is unassailable. German scientist Harald zur Hausen discovered the connection in the 1980s and was awarded a 2008 Nobel Prize for his efforts ([SN: 10/25/08, p. 10](#)). While Pap smears have averted most deaths from cervical cancer in the United States, the malignancy remains a leading cause of women's cancer worldwide. Three shots of Gardasil or Cervarix protect against HPV types responsible for 70 percent of cervical cancers.



HPV vaccines can prevent cervical cancers. Although roughly 40 countries worldwide now have HPV vaccination in their national health guidelines, few low-income countries — where cervical cancer remains a major problem — are in this group. However, pilot programs in some poorer nations indicate that the vaccine is well accepted, particularly when delivered at schools. Source: M. Forouzanfar et al/Lancet 2011, adapted by E. Feliciano

The other half of the equation

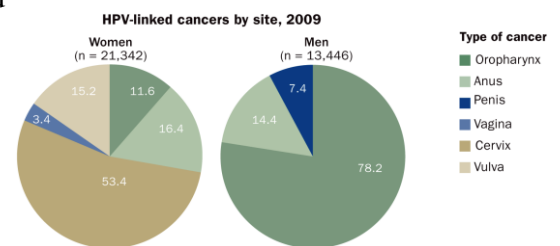
While cervical cancer is the most common malignancy prevented by the vaccines, in the United States nearly two-fifths of HPV-related cancers occur in men. That's because HPV can cause cancers in the mouth or throat areas, and those strike both sexes. HPV is implicated in roughly 60 percent of oral cancers that affect the back of the tongue, throat and tonsils. Although many of these malignancies arise from alcohol and tobacco consumption, those types of cancers have declined in the United States in recent years even as overall oral cancer rates have stayed the same. HPV-related oral cancers account for the rise, particularly in men. In Denmark, the past decade has brought a shift in tonsil cancers, from 43 percent containing HPV to 75 percent. Scientists established a link between oral cancer and HPV more than a decade ago when studies revealed HPV 16 lurking in many oral tumors. In 2007, researchers at Johns Hopkins University found that oral cancer patients were three times as likely as people without the cancer to have had six or more partners on whom they had performed oral sex. But there's much still unknown about the dynamics of oral HPV transmission, says epidemiologist Marc Brisson of Laval University in Quebec. "Kissing may be involved." He and others think that changing sexual practices may be behind the rise in oral cancers.

HPV vaccination is now recommended for boys in the United States ([SN Online: 10/26/11](#)). But because approval came later than it did for girls, only about 8 percent of boys ages 13 to 17, the initial target group, got at least one shot in 2011. As with girls, 11- to 12-year-old boys are the main vaccination target. But teenagers and young adults of both sexes can get the shots as part of a catch-up effort.

The HPV vaccines are given to prevent genital or anal HPV infections. Vaccine companies can't make any claims regarding oral cancer because the vaccines haven't been tested to prevent it. But the evidence is strongly suggestive.

"It's time to start vaccinating boys," says Margaret Stanley, a pathologist at the University of Cambridge in England. Boys and young men in Britain are not yet getting the shots, but Stanley and others are pushing for it. "It will protect 50 percent of the population, and not doing so would be truly discriminatory because that would include gay men, who are very much at risk of anal cancer," she says. "And if you vaccinate boys, you start to get herd immunity."

More than a dozen types of HPV can trigger abnormal tissue growth and malignancy in humans. The cancer burden affects women and men differently, as this chart of U.S. cases demonstrates. Source: A. Jemal et al/JNCI 2013, adapted by E. Feliciano



A shot at the herd

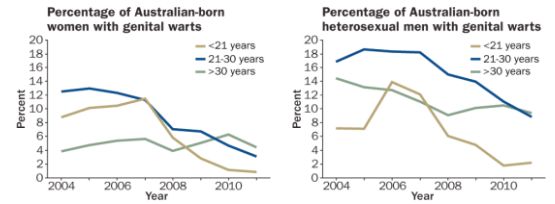
The slow launch of HPV shots in many countries is reminiscent of an earlier campaign that also could have stopped a sexually transmitted virus and the cancer it causes. "With the hepatitis B vaccine, we essentially lost a generation," says Basil Donovan, a sexual health physician at the Kirby Institute and the University of New South Wales in Sydney. Slow implementation since the hepatitis B vaccine became available three decades ago has left the 350 million hepatitis B carriers worldwide at an increased risk of liver cancer.

Similarly, delayed HPV vaccination chalks up a daily cost as more teens become sexually active without protection. About 6 million new genital HPV infections occur each year in the United States, mostly in teens and young adults. Oral HPV infections go uncounted. Canada is faring better, but a study there found that while parents permitted their daughters to get hepatitis B shots in school at an 88 percent rate, only 65 percent consented to HPV vaccination. Germany has lagged behind some other European countries because shortly

after the HPV vaccines were introduced, vaccine opponents raised questions about side effects of the shots.

“Doctors stopped recommending it,” Kaufmann says.

Life is different in Australia. There, public health officials have now documented mass HPV vaccination and the first glimmers of herd immunity. Australian authorities have left little to chance, vaccinating preteen and teenage girls in schools since 2007. They mainly use Gardasil, which prevents genital warts, and such warts are vanishing in young women coming into city clinics. This year Australia began vaccinating boys, too, but herd immunity in them started showing up even before the first shot was fired into a boy’s arm. It seems that protecting girls means protecting boys.



Australia’s school-based program to vaccinate girls against HPV, mainly with Gardasil, is showing benefits for both sexes. Public health officials examining urban clinic records have documented a steady decline in genital warts. The findings hint at herd immunity. Source: H. Ali et al/International Union Against STI World Congress in Melbourne 2012

Australia’s school-based vaccination program, which offers Gardasil free of charge for students, has set the pace for other nations. Between 2007 and 2009, 83 percent of preteen and teenage girls designated for vaccination had gotten at least one shot and 70 percent had received all three. More than half of young adult women got at least one shot, too.

Within two years of the program’s start, the rate of genital warts among girls and women was dropping every quarter at clinics monitored by scientists, Donovan says. Among women under age 21 examined at a eight clinics in Australia in 2011, less than 1 percent had genital warts, compared with more than 8 percent during the pre-vaccination years. Also in 2011, of 235 women who had been vaccinated against HPV, none had any warts, Donovan says. “Warts were a fairly obvious thing to monitor,” he says, since they can appear within months of infection. “In contrast, for cancer it’s measured in decades.”

Updated Australian data were released in late 2012 at conferences in Melbourne and San Juan, Puerto Rico. What really shocked attendees was the finding that genital warts in young men also dropped — from a range of 7 to 14 percent in pre-vaccination years to about 2 percent in 2011 — even though the widespread vaccination of boys hadn’t yet started in Australia.

The findings have changed how some people view HPV vaccination campaigns, Brewer says. “The data in Australia are just jaw-dropping.” Danish researchers recently reported substantial declines in warts as well. Waller says the findings in heterosexual Australian men offer proof that there is herd immunity developing from having vaccinated women in Australia. “That leaves men who have sex with men as the main unprotected group,” she says.

The United States has special problems with school-based vaccination programs because there is no national health insurance that will cover the cost of the vaccine, as is the case in Britain, Canada and Australia. Still, a demonstration project in Denver is investigating a school-based program, says Lauri Markowitz, a medical epidemiologist at the CDC. While states can make vaccinations mandatory for school entry, mandates for HPV are rare, with only schools in Virginia and the District of Columbia requiring the shots.

In the long run, herd immunity remains the goal, and it’s not exotic. Anyone with children sees herd immunity in action. Routine childhood vaccines given to babies nowadays largely maintain herd immunity against scourges that beset previous generations. “The risk is near zero for an individual ever getting polio again,” Zimet says. “We continue to use the Salk vaccine to maintain herd immunity.”

The outlook for HPV may improve in coming years. Markowitz reported at the Puerto Rico meeting that among U.S. teenage girls, the rate of HPV infections of the types covered by the vaccines fell from 11.5 percent before vaccination introduction to 5.1 percent in the years after it, based on a nationwide database. And California public health authorities reported in 2012 that medical records show a substantial decline in genital wart diagnoses in girls in the post-vaccination years and a modest drop in boys.

Also, Merck is testing a new vaccine that covers the four HPV types in Gardasil as well as five others that can cause cancer. Math models suggest it could have a big impact on the HPV infection rate. “This seems like a great step forward,” says Zimet, who expects a nine-type vaccine to get cleared within a year or two.

Such a vaccine would help turn the tide, Stanley says. “You really want to prevent 90 percent of cervical cancers,” she says, “and that’s what it should do. Eventually, you wouldn’t need to screen for them [with a Pap smear]. You’d be looking for a rare disease. We ought to have no cervical cancer in 20 years.”

Other help might come financially. The Affordable Care Act — “Obamacare” — will eventually require insurance plans to cover all recommended vaccines, including HPV.

“The solution to the problem,” says Brewer, “is to improve the public health system we have. It may not rest solely on getting parents to act.” He suggests delivering HPV vaccines in schools and at pharmacies, like flu

shots, and getting doctors to implement a system to recommend them routinely. “One or all of those would work,” he says.

Vaccinating against cancer

There are over a hundred types of human papillomavirus, says Robert Burk, a medical geneticist at the Albert Einstein College of Medicine in New York. But only about a dozen cause the vast majority of HPV-related cancers — and they take years or decades to do it. Still, those few viruses’ stealth makes them dangerous. Over millennia the viruses have perfected the art of colonizing humans and create very little stir when they do.

“In most of us the immune system recognizes the virus and deals with it,” says Margaret Stanley, a pathologist at the University of Cambridge in England. But these viruses can evade people’s immune reactions better than most. In some unlucky few, HPV triggers genetic mutations in the cells it infects, leading to abnormal cell growth and even to cancer. “A fraction of immune systems cannot handle these viruses well,” Stanley says. “We don’t know why.”

The Gardasil and Cervarix vaccines alert the immune system to the two most-studied cancer-causing HPV types, HPV 16 and 18. Together, these two viruses are thought to cause some 70 percent of cervical cancer. The vaccines against them appear effective, with evidence suggesting that even two doses may provide protection. Research has now targeted several other cancer-causing members of the HPV family, and work is under way to test a nine-type vaccine that would add protection against HPV 31, 33, 45, 52 and 58. Gardasil and Cervarix may induce the immune system to develop partial cross-protection against these other HPV types. However, such cross-protection is not as strong as direct immunity.

Basil Donovan of the University of New South Wales in Sydney estimates that by the end of a young woman’s first sexual partnership, she has a 30 percent chance of having acquired an HPV infection. A 2011 study found that 43 percent of sexually active U.S. girls and women up to age 59 were carrying some type of HPV infection. Among U.S. men, the rate was about 50 percent for an HPV infection. In Germany and Denmark, the infection rate is roughly 35 to 40 percent among young women, says Andreas Kaufmann of Charité University Medicine Berlin.

“The vaccine has no effect on existing infections,” Burk cautions. But women who have been vaccinated before being diagnosed with an abnormal cell growth on the cervix — and treated to have the potentially precancerous growth removed — may benefit from that prior vaccination, researchers reported in *BMJ* in 2012. Vaccinated women were about half as likely as their unvaccinated counterparts to be diagnosed with a repeat lesion.

Whether it’s useful to vaccinate a woman after she has cleared a lesion with surgery remains an open question, says gynecologist Kevin Ault of Emory University. But if it does help, those women would be prime candidates for vaccination since they would certainly be members of the unlucky few. — *Nathan Seppa*

1940s

- George Papanicolaou develops Pap smear

1970s

- Harald zur Hausen’s team isolates HPV in genital warts

1980s

- zur Hausen’s team isolates HPV in cervical cancer

- Early vaccine development

1990s

- HPV vaccines developed

- HPV linked to oral cancers

- HPV found in 99.7 percent of cervical cancers

2000s

- Clinical trials of HPV vaccines

- Gardasil recommended for girls and young women (2006)

- zur Hausen wins Nobel Prize (2008)

- Cervarix recommended for girls and young women (2009)

2010s

- HPV vaccines recommended for boys and young men (2011)

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Suggested Reading

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New Camera System Creates High-Resolution 3-D Images from Up to a Kilometer Away **Imaging system that can gather high-resolution, 3-D information about objects that are typically very difficult to image, from up to a kilometer away**

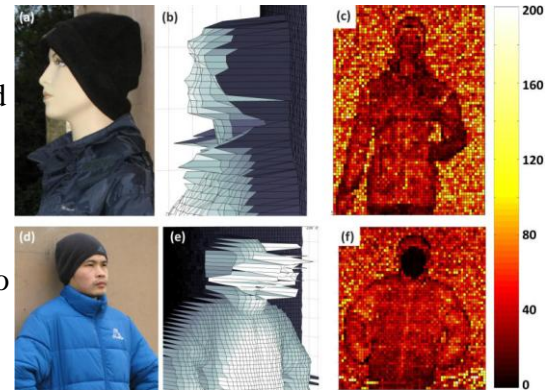
A standard camera takes flat, 2-D pictures. To get 3-D information, such as the distance to a far-away object, scientists can bounce a laser beam off the object and measure how long it takes the light to travel back to a detector. The technique, called time-of-flight (ToF), is already used in machine vision, navigation systems for autonomous vehicles, and other applications, but many current ToF systems have a relatively short range and struggle to image objects that do not reflect laser light well.

A team of Scotland-based physicists has recently tackled these limitations and reported their findings today in the Optical Society's (OSA) open-access journal *Optics Express*.

The research team, led by Gerald Buller, a professor at Heriot-Watt University in Edinburgh, Scotland, describes a ToF imaging system that can gather high-resolution, 3-D information about objects that are typically very difficult to image, from up to a kilometer away.

The new system works by sweeping a low-power infrared laser beam rapidly over an object. It then records, pixel-by-pixel, the round-trip flight time of the photons in the beam as they bounce off the object and arrive back at the source. The system can resolve depth on the millimeter scale over long distances using a detector that can "count" individual photons.

Although other approaches can have exceptional depth resolution, the ability of the new system to image objects like items of clothing that do not easily reflect laser pulses makes it useful in a wider variety of field situations, says Heriot-Watt University Research Fellow Aongus McCarthy, the first author of the Optics Express paper.



3-D images of a mannequin (top) and person (bottom) from 325 meters away. The left-hand panels show close-up photos of the targets taken with a standard camera. In the center are 3-D images of these targets taken by the scanner from 325 meters away. On the right is a color-coded map showing the number of photons that bounce off the targets and return to the detector, with black indicating a low number of photons. Notice that human skin does not show up well using the scanner: the mannequin's face includes depth information, but the person's face does not. (Credit: Optics Express)

"Our approach gives a low-power route to the depth imaging of ordinary, small targets at very long range," McCarthy says. "Whilst it is possible that other depth-ranging techniques will match or out-perform some characteristics of these measurements, this single-photon counting approach gives a unique trade-off between depth resolution, range, data-acquisition time, and laser-power levels."

The primary use of the system is likely to be scanning static, human-made targets, such as vehicles. With some modifications to the image-processing software, it could also determine their speed and direction.

One of the key characteristics of the system is the long wavelength of laser light the researchers chose. The light has a wavelength of 1,560 nanometers, meaning it is longer, or "redder," than visible light, which is only about 380-750 nanometers in wavelength. This long-wavelength light travels more easily through the atmosphere, is not drowned out by sunlight, and is safe for eyes at low power.

Many previous ToF systems could not detect the extra-long wavelengths that the Scottish team's device is specially designed to sense.

The scanner is particularly good at identifying objects hidden behind clutter, such as foliage. However, it cannot render human faces, instead drawing them as dark, featureless areas. This is because at the long wavelength used by the system, human skin does not reflect back a large enough number of photons to obtain a depth measurement.

However, the reflectivity of skin can change under different circumstances. "Some reports indicate that humans under duress -- for example, with perspiring skin -- will have significantly greater return signals," and thus should produce better images, McCarthy says.

Outside of target identification, photon-counting depth imaging could be used for a number of scientific purposes, including the remote examination of the health and volume of vegetation and the movement of rock faces, to assess potential hazards.

Ultimately, McCarthy says, it could scan and image objects located as far as 10 kilometers away. "It is clear that the system would have to be miniaturized and ruggedized, but we believe that a lightweight, fully portable scanning depth imager is possible and could be a product in less than five years."

Next steps for the team include making the scanner work faster. Although the data for the high-resolution depth images can be acquired in a matter of seconds, currently it takes about five to six minutes from the onset of scanning until a depth image is created by the system.

Most of that lag, McCarthy says, is due to the relatively slow processing time of the team's available computer resources. "We are working on reducing this time by using a solid-state drive and a higher specification computer, which could reduce the total time to well under a minute. In the longer term, the use of more dedicated processors will further reduce this time."

The research was funded by the United Kingdom's Engineering and Physical Sciences Research Council.

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<http://www.bbc.co.uk/news/health-22029708>

Roche agrees to release all trial data on Tamiflu drug

The drug company Roche, which makes Tamiflu, has announced it will give researchers access to all its trial data for the influenza drug, the BMJ reports.

Roche had previously been criticised for failing to grant access to the results of all its 74 trials.

In an email it said it would provide the information over the next few months.

Campaigners say Roche should not have delayed access to the data.

It is estimated that half of all clinical trials have never been published and positive trial results are twice as likely to be published as negative findings.

The AllTrials campaign wants the pharmaceutical industry to publish all data, and is supported by the Wellcome Trust, the British Medical Journal and NICE.

In December 2009, Roche gave the Cochrane group - an internationally renowned human health care and policy research body - access to one part of just 10 Tamiflu trials. There are 74 in total.

Then in February, Roche pledged to give researchers access to more of its trial data.

Finally this week, in an email to the Cochrane researchers, Roche said it had decided to provide "each CSR [clinical study report]" over the next few months.

Persistence

Another drug company GlaxoSmithKline recently decided to release 30 clinical study reports on its influenza drug zanamivir (Relenza) to the same Cochrane group.

Sile Lane, director of campaigns at Sense about Science, an organisation which helped to start the campaign for all drug trial data to be released, said: "It shouldn't have taken the researchers years of persistence and publicity to get [access to] these Tamiflu results."

The Cochrane group have cautiously welcomed the move.

But they are concerned that data redaction and other problems may make analysis and interpretation impossible. They also point out that Roche has previously promised access to data and not delivered.

A spokesman for Roche confirmed that it had granted researchers access to clinical study reports for "all 74 Roche-sponsored clinical trials on Tamiflu".

"By amending the data transparency policy, Roche has taken a leading role in improving access to clinical trial data for third party researchers.

"We understand and support calls for our industry to be more transparent about clinical trial data with the aim of meeting the best interests of patients and medicine."

http://www.sciencenews.org/view/generic/id/349372/description/Dream_contents_deciphered_by_computer

Dream contents deciphered by computer

Similar brain patterns emerge when seeing an object and conjuring it during sleep

By Rachel Ehrenberg

A computer can decode the stuff of dreams. By comparing brain activity during sleep with activity patterns collected while study participants looked at certain objects, a computer learned to identify some contents of people's unconscious reveries.

"It's striking work," says cognitive psychologist Frank Tong of Vanderbilt University in Nashville, who was not involved in the research. "It's a demonstration that brain activity during dreaming is very similar to activity during wakefulness."

The work, reported April 4 in *Science* by Japanese researchers led by Yukiyasu Kamitani of Advanced Telecommunications Research Institute International, adds to somewhat scant knowledge of how the brain constructs dreams, says Tong. The research could lead to a better understanding of what the brain does during different states of consciousness, such as those experienced by some coma patients.

Dreams are a bit of a black box and difficult to study. Experiments with mice have revealed aspects of sleep and dreaming, such as how the experiences contribute to forming memories. But a mouse can't tell you what it dreamed about. And the sleep stage that's richest in dreams — REM sleep — typically kicks in about 90 minutes after a person conks out, making it time consuming to gather data on dreams. The noisy fMRI brain scanning machine doesn't help.

To skirt these experimental issues, the researchers recorded brain activity in three adult male volunteers during the early stages of sleep. After the subjects had dozed off, they were repeatedly awakened and asked for detailed reports on what they had seen while sleeping. In an example, one participant stated: "Well, there were persons, about three persons, inside some sort of hall. There was a male, a female and maybe like a child. Ah, it was like a boy, a girl and a mother. I don't think that there was any color."

After gathering at least 200 such reports from the three men, the researchers used a lexical database to group the dreamed objects in coarse categories, such as street, furniture and girl. Then the study participants looked at images of things in those categories, while their brains were again scanned. Computer algorithms sorted through these patterns of brain activity, linking particular patterns with objects.

When the computer went back to the brain scans taken during dreaming, it did a pretty good job of distinguishing some of the signals, such as whether a dream contained a book or a girl. On average, the computer could pick which of two objects had appeared in a dream 70 percent of the time, a rate that is much better than would be expected by chance.

"To be able to get enough data to do this kind of analysis is really impressive," says Russell Poldrack, a neuroimaging expert at the University of Texas at Austin.

The study bolsters the notion that the vivid imagery of dreams, no matter how fantastic, is as real as waking life, Kamitani says, at least from the brain's perspective. Further research may reveal if the same is true about other dreamed senses, such as experienced sounds or emotions.

After monitoring a man's brain activity while he looked various kinds of objects (top images), scientists trained a computer to decode patterns of brain activity recorded while the man dreamed. The computer could distinguish among many dreamed objects. The size of the word in the word cloud (bottom) indicates the likelihood that that object was in the dream.

T. Horikawa et al. *Neural decoding of visual imagery during sleep*. *Science*. doi:10.1126/science.1234330. [[Go to\]](#)

<http://www.sciencedaily.com/releases/2013/04/130405064027.htm>

How Life May Have First Emerged On Earth: Foldable Proteins in a High-Salt Environment

New research has yielded data supporting the idea that 10 amino acids believed to exist on Earth around 4 billion years ago were capable of forming foldable proteins in a high-salt (halophile) environment.

A structural biologist at the Florida State University College of Medicine has made discoveries that could lead scientists a step closer to understanding how life first emerged on Earth billions of years ago.

Professor Michael Blaber and his team produced data supporting the idea that 10 amino acids believed to exist on Earth around 4 billion years ago were capable of forming foldable proteins in a high-salt (halophile) environment. Such proteins would have been capable of providing metabolic activity for the first living organisms to emerge on the planet between 3.5 and 3.9 billion years ago.

The results of Blaber's three-year study, which was built around investigative techniques that took more than 17 years to develop, are published in the journal *Proceedings of the National Academy of Sciences*.

The first living organisms would have been microscopic, cell-like organizations capable of replicating and adapting to environmental conditions -- a humble beginning to life on Earth. "The current paradigm on the emergence of life is that RNA came first and in a high-temperature environment," Blaber said. "The data we are generating are much more in favor of a protein-first view in a halophile environment."

The widely accepted view among scientists is that RNA, found in all living cells, would have likely represented the first molecules of life, hypothesizing an "RNA-first" view of the origin of living systems from non-living molecules. Blaber's results indicate that the set of amino acids produced by simple chemical processes contains the requisite information to produce complex folded proteins, which supports an opposing "protein-first" view. Another prevailing view holds that a high-temperature (thermophile) environment, such as deep-ocean thermal vents, may have been the breeding ground for the origin of life. "The halophile, or salt-loving, environment has typically been considered one that life adapted into, not started in," Blaber said. "Our study of the prebiotic amino acids and protein design and folding suggests the opposite."

Without the ability to fold, proteins would not be able to form the precise structures essential for functions that sustain life as we know it. Folding allows proteins to take on a globular shape through which they can interact with other proteins, perform specific chemical reactions, and adapt to enable organisms to exploit a given environment.

"There are numerous niches that life can evolve into," Blaber said. "For example, extremophiles are organisms that exist in high temperatures, high acidity, extreme cold, extreme pressure and extreme salt and so on. For life to exist in such environments it is essential that proteins are able to adapt in those conditions. In other words, they have to be able to fold."

Comet and meteorite fragments, like those that recently struck in the Urals region of Russia, have provided evidence regarding the arrival of amino acids on Earth. Such fragments predate Earth and would have been responsible for delivering a set of 10 prebiotic (before life) amino acids, whose origins are in the formation of our solar system.

Today the human body uses 20 common amino acids to make all its proteins. Ten of those emerged through biosynthetic pathways -- the way living systems evolve. Ten -- the prebiotic set -- can be made by chemical reactions without requiring any living system or biosynthetic pathway.

Scientific evidence exists to support many elements in theories of abiogenesis (the emergence of life), including the time frame (around 3.5 to 3.9 billion years ago) and the conditions on Earth and in its atmosphere at that time. Earth would have been made up of volcanic land masses (the beginning of the formation of continents), salty oceans and fresh-water ponds, along with a hot (around 80 degrees Celsius) and steamy atmosphere comprising carbon dioxide and nitrogen. Oxygen would have come later as a by-product of green plant life and bacteria that emerged.

Using a technique called top-down symmetric deconstruction, Blaber's lab has been able to identify small peptide building blocks capable of spontaneous assembly into specific and complex protein architectures. His recent work explored whether such building blocks can be composed of only the 10 prebiotic amino acids and still fold. His team has achieved foldability in proteins down to 12 amino acids -- about 80 percent of the way to proving his hypothesis.

If Blaber's theory holds, scientists may refocus where they look for evidence in the quest to understand where, and how, life began. "Rather than a curious niche that life evolved into, the halophile environment now may take center stage as the likely location for key aspects of abiogenesis," he said. "Likewise, the role of the formation of proteins takes on additional importance in the earliest steps in the beginnings of life on Earth."

L. M. Longo, J. Lee, M. Blaber. Simplified protein design biased for prebiotic amino acids yields a foldable, halophilic protein. Proceedings of the National Academy of Sciences, 2013; 110 (6): 2135 DOI: 10.1073/pnas.1219530110

<http://phys.org/news/2013-04-mosquitos-larger-dime-painful-invade.html>

Researcher says mosquitos, larger than a dime and packing a painful bite, could invade soon

It's just a matter of time before the "gallinipper" or flying, "hairy legged-zebra" takes the stage

With plenty of news reports talking about giant mosquitos invading Florida, Deby Cassill, a biologist at the University of South Florida St. Petersburg, said it's just a matter of time before the "gallinipper" or flying, "hairy legged-zebra" take the stage. "So we've got this huge potential with all of these eggs that were laid during Tropical Storm Debbie, the next storm coming in that wets that surface, we're going to have a huge population explosion of this giant mosquito," said Cassill.

The American Giant Mosquito or *Psorophora ciliata* are known as floodwater mosquitoes because they lay their eggs in low-lying areas with damp soil and grassy overgrowth. When these areas flood following a dry period, large numbers of adult mosquitoes will hatch.

They have been around for centuries and are notorious for inflicting a painful bite. It is only the females that attack. And they do it during both the day and night -- in stark contrast to the typical dusk and dawn flights of smaller species of mosquitoes.

According to Cassill, the animal originates near the area of the Mississippi river delta and with heavy rains during previous tropical storms, migrated over to Florida.

"They've been called the hairy-legged zebra of the mosquito world and I think that they are not as big as a quarter. But their legs are long enough and their bodies are long enough to span a dime and in the mosquito world, that's a big animal, kind of like a dinosaur or a large vampire floating around and going after us."

The bite from these mosquitos feels more intense than that of the smaller types because the giants have saw-like mouthparts that inject saliva and create intense pain when extracting the jaw after the bite.

Cassill said the critters do not carry disease, but they consume the larvae of other types of disease-carrying mosquitos. And, they don't move around that fast.

"What they go after actually is they have carbon dioxide or CO2 detectors and when they smell the breath of humans or the breath of cattle or the breath of live stock, that is one of the long distance detectors. When they are close enough, they use their vision. Then after that they have little heat detectors and they'll go for the warm spots along the throat, behind the knees, sometimes behind the neck and zero in and poke that long jaw into our bodies."

According to Cassill, the best protection from the American Giant Mosquito is an old technology.

"I think just be aware of it, have your fly swatter or mosquito swatter. I mean somebody ought to have a giant mosquito swatter in place by then."

Ultimately, they are among certain pests that we may just have to coexist with, she said, if we want to live in Florida.

"Other than that there is not much we can do. There is no way that we can rid ourselves of all pests. Part of it is we live in paradise, there is a small cost and the American Giant Mosquito may be that cost, for a short time. "

http://www.eurekalert.org/pub_releases/2013-04/uoea-bin040513.php

Breakthrough in neuroscience could help re-wire appetite control

Discovery in neuroscience that could offer a long-lasting solution to obesity

Researchers at the University of East Anglia (UEA) have made a discovery in neuroscience that could offer a long-lasting solution to eating disorders such as obesity.

It was previously thought that the nerve cells in the brain associated with appetite regulation were generated entirely during an embryo's development in the womb and therefore their numbers were fixed for life.

But research published today in the Journal of Neuroscience has identified a population of stem cells capable of generating new appetite-regulating neurons in the brains of young and adult rodents.

Obesity has reached epidemic proportions globally. More than 1.4 billion adults worldwide are overweight and more than half a billion are obese. Associated health problems include type 2 diabetes, heart disease, arthritis and cancer. And at least 2.8 million people die each year as a result of being overweight or obese.

The economic burden on the NHS in the UK is estimated to be more than £5 billion annually. In the US, the healthcare cost tops \$60 billion.

Scientists at UEA investigated the hypothalamus section of the brain – which regulates sleep and wake cycles, energy expenditure, appetite, thirst, hormone release and many other critical biological functions. The study looked specifically at the nerve cells that regulate appetite.

The researchers used 'genetic fate mapping' techniques to make their discovery – a method that tracks the development of stem cells and cells derived from them, at desired time points during the life of an animal.

They established that a population of brain cells called 'tanycytes' behave like stem cells and add new neurons to the appetite-regulating circuitry of the mouse brain after birth and into adulthood.

Lead researcher Dr Mohammad K. Hajihosseini, from UEA's school of Biological Sciences, said: "Unlike dieting, translation of this discovery could eventually offer a permanent solution for tackling obesity.

"Loss or malfunctioning of neurons in the hypothalamus is the prime cause of eating disorders such as obesity.

"Until recently we thought that all of these nerve cells were generated during the embryonic period and so the circuitry that controls appetite was fixed. "But this study has shown that the neural circuitry that controls

appetite is not fixed in number and could possibly be manipulated numerically to tackle eating disorders.

"The next step is to define the group of genes and cellular processes that regulate the behaviour and activity of tanycytes. This information will further our understanding of brain stem cells and could be exploited to develop drugs that can modulate the number or functioning of appetite-regulating neurons.

"Our long-term goal of course is to translate this work to humans, which could take up to five or 10 years. It could lead to a permanent intervention in infancy for those predisposed to obesity, or later in life as the disease becomes apparent."

The research was funded by the Wellcome Trust.

'Fgf10-expressing tanycytes add new neurons to the appetite/energy-balance regulating centres of the postnatal and adult hypothalamus' by Mohammad Hajihosseini, Niels Haan, Timothy Goodman, Alaleh Najdi-Samiei and Christina Stratford (all UEA), Ritva Rice (University of Helsinki), Elie El Agha and Saverio Bellusci (both University of Giessen) is published by the Journal of Neuroscience.

http://www.eurekalert.org/pub_releases/2013-04/gsoa-fma032913.php

Flies model a potential sweet treatment for Parkinson's disease

Research presented at the Genetics Society of America's ongoing annual Drosophila Conference in Washington, D.C., suggests that mannitol, a sugar substitute, could lead to a future treatment for Parkinson's disease

Washington, D.C - Researchers from Tel Aviv University describe experiments that could lead to a new approach for treating Parkinson's disease (PD) using a common sweetener, mannitol. This research is presented today at the Genetics Society of America's 54th Annual Drosophila Research Conference in Washington D.C., April 3-7, 2013.

Mannitol is a sugar alcohol familiar as a component of sugar-free gum and candies. Originally isolated from flowering ash, mannitol is believed to have been the "manna" that rained down from the heavens in biblical times. Fungi, bacteria, algae, and plants make mannitol, but the human body can't. For most commercial uses it is extracted from seaweed although chemists can synthesize it. And it can be used for more than just a sweetener.

The Food and Drug Administration approved mannitol as an intravenous diuretic to flush out excess fluid. It also enables drugs to cross the blood-brain barrier (BBB), the tightly linked cells that form the walls of capillaries in the brain. The tight junctions holding together the cells of these tiniest blood vessels come slightly apart five minutes after an infusion of mannitol into the carotid artery, and they stay open for about 30 minutes.

Mannitol has another, less-explored talent: preventing a sticky protein called α -synuclein from gumming up the substantia nigra part of the brains of people with PD and Lewy body dementia (LBD), which has similar symptoms to PD. In the disease state, the proteins first misfold, then form sheets that aggregate and then extend, forming gummy fibrils.

Certain biochemicals, called molecular chaperones, normally stabilize proteins and help them fold into their native three-dimensional forms, which are essential to their functions. Mannitol is a chemical chaperone. So like a delivery person who both opens the door and brings in the pizza, mannitol may be used to treat Parkinson's disease by getting into the brain and then restoring normal folding to α -synuclein.

Daniel Segal, PhD, and colleagues at Tel Aviv University investigated the effects of mannitol on the brain by feeding it to fruit flies with a form of PD that has highly aggregated α -synuclein.

The researchers used a "locomotion climbing assay" to study fly movement. Normal flies scamper right up the wall of a test tube, but flies whose brains are encumbered with α -synuclein aggregates stay at the bottom, presumably because they can't move normally. The percentage of flies that climb one centimeter in 18 seconds assesses the effect of mannitol.

An experimental run tested flies daily for 27 days. After that time, 72% of normal flies climbed up, in comparison to 38% of the PD flies. Their lack of ascension up the sides of the test tube indicated "severe motor dysfunction."

In contrast, were flies bred to harbor the human mutant α -synuclein gene, who as larvae feasted on mannitol that sweetened the medium at the bottoms of their vials. These flies fared much better -- 70% of them could climb after 27 days. And slices of their brains revealed a 70% decrease in accumulated misfolded protein compared to the brains of mutant flies raised on the regular medium lacking mannitol.

It's a long way from helping climbing-impaired flies to a new treatment for people, but the research suggests a possible novel therapeutic direction. Dr. Segal, however, cautioned that people with PD or similar movement disorders should not chew a ton of mannitol-sweetened gum or sweets; that will not help their current condition. The next step for researchers is to demonstrate a rescue effect in mice, similar to improved climbing by flies, in which a rolling drum ("rotarod") activity assesses mobility.

"Until and if mannitol is proven to be efficient for PD on its own, the more conservative and possibly more immediate use can be the conventional one, using it as a BBB disruptor to facilitate entrance of other approved drugs that have problems passing through the BBB," Dr. Segal said. A preliminary clinical trial of mannitol on a small number of volunteers might follow if results in mice support those seen in the flies, he added, but that is still many research steps away.

Mannitol - a BBB disrupter is also a potent α -synuclein aggregation inhibitor for treating Parkinson's disease. Daniel Segal^{1,2}, Ronit Shaltiel-Karyo¹, Moran Frenkel-Pinter¹, Edward Rockenstein³, Christina Patrick³, Michal Levy-Sakin¹, Nirit Egoz-Matia¹, Eliezer Masliah³, Ehud Gazit¹. 1) Department of Molecular Microbiol & Biotech, Tel Aviv University, Tel Aviv 69978, Israel; 2) Sagol School of Neurosciences, Tel Aviv University, Tel Aviv 69978, Israel; 3) Department of Neurosciences, School of Medicine, University of California at San Diego, La Jolla, CA 92093, USA.

http://www.eurekalert.org/pub_releases/2013-04/uops-toc040513.php

2-step ovarian cancer immunotherapy made from patients' own tumor shows promise

Trial benefits three-quarters of patients

WASHINGTON, D.C. — As many as three quarters of advanced ovarian cancer patients appeared to respond to a new two-step immunotherapy approach -- including one patient who achieved complete remission -- according research from the Perelman School of Medicine at the University of Pennsylvania that will be presented today in a press conference at the AACR Annual Meeting 2013 (Presentation #LB-335).

The immunotherapy has two steps – a personalized dendritic cell vaccination and adoptive T-cell therapy. The team reports that in the study of 31 patients, vaccination therapy alone showed about a 61 percent clinical benefit, and the combination of both therapies showed about a 75 percent benefit.

The findings offer new hope for the large number of ovarian cancer patients who relapse following treatment.

The first step of the immunotherapy approach is to preserve the patient's tumor cells alive, using sterile techniques at the time of surgery so they can be used to manufacture a personalized vaccine that teaches the patient's own immune system to attack the tumor. Then, the Penn Medicine team isolates immune cells called dendritic cells from patients' blood through a process called apheresis, which is similar to the process used for blood donation. Researchers then prepare each patient's personalized vaccine by exposing her dendritic cells to the tumor tissue that was collected during surgery.

Because ovarian cancer symptoms can be stealth and easily mistaken for other issues – constipation, weight gain, bloating, or more frequent urination – more than 60 percent of patients are diagnosed only after the disease has spread to their lymph nodes or other distant sites in the body, when treatment is much less likely to

produce a cure compared to when the disease is detected early. As the fifth leading cause of cancer-related deaths among women in the United States, it takes the lives of more than 14,000 women each year.

"Given these grim outcomes, there is definitely a vast unmet need for the development of novel, alternate therapies," said lead author Lana Kandalaft, PharmD, PhD, MTR, a research assistant professor of Obstetrics and Gynecology and director of clinical development and operations in Penn Medicine's Ovarian Cancer Research Center. "This is the first time such a combination immunotherapy approach has been used for patients with ovarian cancer, and we believe the results are leading us toward a completely new way to treat this disease."

Both treatments are given in conjunction with bevacizumab, a drug that controls the blood vessel growth that feeds tumors. Combining bevacizumab with immunotherapy makes a powerful duo, Kandalaft says. The vaccine trial is still open to accrual to test new combinatorial strategies.

The other Penn authors are Janos Tanyi, Cheryl Chiang, Daniel Powell, and George Coukos. This study was funded by a National Cancer Institute Ovarian Specialized Program of Research Excellence grant, the National Institutes of Health and the Ovarian Cancer Immunotherapy Initiative.

<http://www.bbc.co.uk/news/health-22042994>

'Absurd' drug laws 'hinder research' - Prof David Nutt

'Absurd' laws dealing with magic mushrooms, ecstasy and cannabis are hindering medical research, according to a former government drugs adviser.

By James Gallagher Health and science reporter, BBC News

Prof David Nutt says he has funding to research the use of the chemical psilocybin - found in fungi known as "magic mushrooms" to treat depression. But he says "insane" regulations mean he cannot get hold of the drug.

The Home Office said there was "no evidence" that regulations were a barrier to research. It is not the first time Prof Nutt has been at odds with government policy. He was sacked as an adviser over views that ecstasy and LSD were less harmful than alcohol. Psilocybin is illegal in the UK and is a Class A drug.



Psilocybin is a hallucinogenic chemical in magic mushrooms

Earlier research at Imperial College London showed that injections of psilocybin could calm a region of the brain which is overactive in depression. The group is now trying to conduct a clinical trial to test psilocybin as a treatment.

Stumbling block

The UK's Medical Research Council has given the lab a £550,000 grant to test the idea - in 30 patients who have not responded to at least two other therapies. They have also been given ethical approval.

However, there are more stringent regulations for testing the drug as a treatment than in earlier experiments. As a potential medicine it must meet Good Manufacturing Practice requirements set out by the EU.

"It hasn't started yet because the big problem is getting hold of the drug," said Prof Nutt. He said finding a company to provide a clinical-grade psilocybin had "yet proved impossible" as none was prepared to "go through the regulatory hoops".

"So we are between a rock and a hard place, which is very unfortunate, because if this is an effective treatment for patients then they're obviously being denied that possibility so one of the things we have to do now is have a more rational debate about the way the drugs laws are being implemented."

He will tell the British Neuroscience Association that similar rules are hampering research into other drugs such as ecstasy and cannabis.

Ahead of the meeting he told the BBC: "We have regulations which are 50 years old, have never been reviewed and they are holding us back, they're stopping us doing the science and I think it's a disgrace actually."

A Home Office spokesman said: "Our licensing regime enables legitimate research to take place while ensuring that harmful drugs don't get into the hands of criminals. "We have no evidence to suggest that the current listing of psilocybin as a schedule one substance is a barrier to attracting funding for legitimate research."

http://www.eurekalert.org/pub_releases/2013-04/acs-dci031813.php

Do cells in the blood, heart and lungs smell the food we eat?

Heart, blood, lung and other cells in the body have same receptors for sensing odors that exist in the nose

NEW ORLEANS - In a discovery suggesting that odors may have a far more important role in life than previously believed, scientists have found that heart, blood, lung and other cells in the body have the same receptors for sensing odors that exist in the nose. It opens the door to questions about whether the heart, for instance, "smells" that fresh-brewed cup of coffee or cinnamon bun, according to the research leader, who spoke here

today at the 245th National Meeting & Exposition of the American Chemical Society, the world's largest scientific society.

Peter Schieberle, Ph.D., an international authority on food chemistry and technology, explained that scientists thought that the nose had a monopoly on olfactory receptors. Located on special cells in the mucus-covered olfactory epithelium in the back of the nose, olfactory receptors are docking ports for the airborne chemical compounds responsible for the smell of food and other substances. Those molecules connect with the receptors, triggering a chain of biochemical events that register in the brain as specific odors. But discovery of olfactory receptors on other, non-olfactory cells came as a surprise.

"Our team recently discovered that blood cells — not only cells in the nose — have odorant receptors," said Schieberle. "In the nose, these so-called receptors sense substances called odorants and translate them into an aroma that we interpret as pleasing or not pleasing in the brain. But surprisingly, there is growing evidence that also the heart, the lungs and many other non-olfactory organs have these receptors. And once a food is eaten, its components move from the stomach into the bloodstream. But does this mean that, for instance, the heart 'smells' the steak you just ate? We don't know the answer to that question."

His team recently found that primary blood cells isolated from human blood samples are attracted to the odorant molecules responsible for producing a certain aroma. Schieberle described one experiment in which scientists put an attractant odorant compound on one side of a partitioned multi-well chamber, and blood cells on the other side. The blood cells moved toward the odor.

"Once odor components are inside the body, however, it is unclear whether they are functioning in the same way as they do in the nose," he stated. "But we would like to find out."

Schieberle's group and colleagues at the Technical University of Munich work in a field termed "sensomics," which focuses on understanding exactly how the mouth and the nose sense key aroma, taste and texture compounds in foods, especially comfort foods like chocolate and roasted coffee.

For example, baked beans and beans in foods like chili provide a "full," rich mouth-feel. Adding the component of beans responsible for this texture to another food could give it the same sensation in the mouth, he explained. Natural components also can interact with substances in foods to create new sensations.

The researchers use sensomics to better understand why foods taste, feel and smell appetizing or unappetizing. They use laboratory instruments to pick apart the chemical components. They then put those components together in different combinations and give these versions to human taste-testers who evaluate the foods. In this way, they discovered that although coffee contains 1,000 potential odor components, only 25 actually interact with an odor receptor in the nose and are smelled.

"Receptors help us sense flavors and aromas in the mouth and nose," said Schieberle. "These receptors are called G-protein-coupled receptors, and they were the topic of the Nobel Prize in Chemistry in 2012. They translate these sensations into a perception in the brain telling us about the qualities of a food." Odorant receptors and the organization of the olfactory system also were the topic of the 2004 Nobel Prize in Medicine. Of the total of around 1,000 receptors in the human body, about 800 of these are G-protein-coupled receptors, he said. Half of these G-protein-coupled receptors sense and translate aromas. But only 27 taste receptors exist. And although much research in the food industry has gone into identifying food components, little effort has focused on the tying those components to flavor perceptions until now, he said.

<http://bit.ly/10MoA19>

Red meat boosts gut bugs that raise heart disease risk

Red meat gives a boost to gut bugs that are bad news for your arteries. The discovery may explain why eating lots of meat increases the risk of heart disease.

18:00 07 April 2013 by Rebecca Summers

Stanley Hazen at the Cleveland Clinic Lerner Research Institute in Ohio and colleagues fed mice a diet high in carnitine, a nutrient found in large amounts in red meat and also added to energy drinks. The team found that this increased the incidence of atherosclerosis, a thickening of the artery walls. However, when the researchers fed the same diet to mice with suppressed gut flora, they saw no increase in atherosclerosis.

A similar effect appears to exist in humans. The team studied a group of people undergoing cardiac evaluation, and found that those who had higher levels of carnitine in their blood also had a higher incidence of previous cardiac problems.

Bacteria boost

Some bacteria in the intestine use carnitine as an energy source, breaking it down and producing a waste product called trimethylamine (TMA). The liver converts this into another substance, trimethylamine-N-oxide (TMAO), which is excreted in urine.

In mice, high levels of dietary carnitine shifted the types of bacteria present in the gut and increased the volume of TMAO produced tenfold. "Imagine a Petri dish full of bacteria," says Hazen. "If you start feeding them carnitine, the ones that like carnitine more will reproduce and those that don't will decrease."

TMAO levels matter because the substance increases the uptake of "bad" cholesterol and prevents its destruction by macrophages – white blood cells – in artery walls. This causes a build-up of plaque that can lead to atherosclerosis.

In further tests, Hazen's team found that meat-eaters produced higher levels of TMAO than vegans or vegetarians after they were fed carnitine, suggesting that they had more TMA-producing bacteria in their gut. "I'm not telling people to cut out red meat," Hazen says. "But cut down the frequency and portion sizes."

Too much of a good thing

Carnitine has its good side: it transports fuel into mitochondria, a cell's powerhouses. "A bit like stoking a fire, carnitine shovels fatty acid into the mitochondrial furnace," says Hazen.

As our body makes all of the carnitine it needs, any additional intake – for example, in energy drinks or commercially available carnitine supplements – has no significant benefit. Evidence that increasing carnitine intake gives you more energy is weak, Hazen says. He adds that the new work suggests that taking carnitine supplements could in fact alter your metabolism to increase risk of cardiovascular disease.

"This is impressive work that may help to explain the association seen in epidemiological studies between red meat consumption and coronary heart disease," says David Leake at the University of Reading, UK, who studies atherosclerosis. "However it will require a lot more work to prove how important the role of TMAO is in cardiovascular disease in humans."

Hazen hopes to have a diagnostic test for TMAO ready by the end of the year so that doctors could monitor TMAO just like keeping tabs on high cholesterol. This will be useful if TMAO levels in the blood are indeed a precursor for the onset of atherosclerosis. *Journal reference: Nature Medicine, DOI: 10.1038/nm.3145*

<http://www.sciencedaily.com/releases/2013/04/130407133241.htm>

Global Burden of Dengue Is Triple Current Estimates

The global burden of dengue infection is more than triple current estimates from the World Health Organization, according to a multinational study published today in the journal Nature.

The research has created the first detailed and up-to-date map of dengue distribution worldwide, enabling researchers to estimate the total numbers of people affected by the virus globally, regionally and nationally. The findings will help to guide efforts in vaccine, drug and vector control strategies.

The study was led by Professor Simon Hay, a Wellcome Trust Senior Research Fellow at the University of Oxford, as part of the International Research Consortium on Dengue Risk Assessment, Management and Surveillance.

Dengue, also known as 'breakbone fever', is a viral infection that is transmitted between humans by mosquitoes. In some people, it causes life-threatening illness.

There are currently no licensed vaccines or specific treatments for dengue, and substantial efforts to control the mosquitoes that transmit the disease have not stopped its rapid emergence and global spread. Until now, little was known about the current distribution of the risk of dengue virus infection and its public health burden around the world.

Dr Samir Bhatt, who led the modelling for the study, says: "Our aim was to take all of the evidence that is currently available on the distribution of dengue worldwide and combine it with the latest in mapping and mathematical modelling to produce the most refined risk maps and burden estimates. We then hope to use this knowledge to help predict the future burden of the disease."

The findings reveal that dengue is ubiquitous throughout the tropics, with local spatial variations in risk influenced strongly by rainfall, temperature and urbanisation. The team estimate that there are 390 million dengue infections across the globe each year, of which 96 million reach any level of clinical or subclinical severity. This is more than triple the WHO's most recent estimates of 50-100 million infections per year. Professor Simon Hay explains: "We found that climate and population spread were important factors for predicting the current risk of dengue around the world. With globalisation and the constant march of urbanisation, we anticipate that there could be dramatic shifts in the distribution of the disease in the future: the virus may be introduced to areas that previously were not at risk, and those that are currently affected may experience increases in the number of infections."

"We hope that the research will initiate a wider discussion about the significant global impact of this disease." Of the 96 million apparent infections, Asia bore 70 per cent of the burden. India alone accounted for around one-third of all infections. The results indicate that with 16 million infections, Africa's burden is almost

equivalent to that of the Americas and is significantly larger than previously appreciated. The authors suggest that the hidden African dengue burden could be a result of the disease being masked by symptomatically similar illnesses, under-reporting and highly variable treatment-seeking behaviour.

Professor Jeremy Farrar, Director of the Wellcome Trust Vietnam Research Programme and Oxford University Clinical Research Unit Hospital for Tropical Diseases in Vietnam, explains that the map and estimates produced by Hay's group set the benchmark for the disease: "This is the first systematic robust estimate of the extent of dengue. The evidence that we've gathered here will help to maximise the value and cost-effectiveness of public health and clinical efforts, by indicating where limited resources can be targeted for maximum possible impact

With endemic transmission in Asia and the Americas, recent outbreaks in Portugal, the ever-increasing incidence in Africa, and the challenges of making an effective dengue vaccine or controlling the vector, Professor Farrar stresses: "This really does represent a crucial period in the global spread of dengue."

Jimmy Whitworth, Head of International Activities at the Wellcome Trust, said: "Over time, this comprehensive map of global disease burden will also help to demonstrate which control measures are making the biggest difference in reducing the number of people suffering from dengue infection. Without a vaccine or specific treatment options, it's crucial that we understand where best to direct the limited resources available for preventing this resurgent disease."

Samir Bhatt, Peter W. Gething, Oliver J. Brady, Jane P. Messina, Andrew W. Farlow, Catherine L. Moyes, John M. Drake, John S. Brownstein, Anne G. Hoen, Osman Sankoh, Monica F. Myers, Dylan B. George, Thomas Jaenisch, G. R. William Wint, Cameron P. Simmons, Thomas W. Scott, Jeremy J. Farrar, Simon I. Hay. The global distribution and burden of dengue. Nature, 2013; DOI: 10.1038/nature12060