http://phys.org/news/2014-03-scientists-neutral-discoveries.html#rssowlmlink

Scientists can't claim to be neutral about their discoveries

There is an enormous gap between the effects and consequences of science, and how much scientists consider these consequences. This is dangerous, but there is something we can do about it.

There is no pursuit of knowledge that does not seek to affect the world. Science is made by people with interests, intentions and ambitions; and it's funded by governments and companies with agendas. Scientific development is subject to funding rules, to expectations about outcomes, and to social forces and institutions that shape our research.

In the 1950s, Jonas Salk gave a striking answer to the question: "Who owns the patent on this vaccine?" He said:

There is no patent. Could you patent the sun?

Salk's immortal words refer to the patent for the polio vaccine that he helped develop. These words are worth remembering not just because his position proved right, but because the question was tremendously important: can a scientist accept privatising knowledge that would benefit all?

There are usually two lines of thought on this. The privatisation argument is that without the subsequent benefit of monopoly pricing, firms would not invest in development of new and socially beneficial products. The argument against it is that restricting others from using and improving technology that should be in the public domain stifles innovation and development of new products.

And the issue is not a minor one: for example, Novartis recently tried to block the manufacturing of a generic lifesaving drug in India that helps treat cancer patients. This is one of the consequences of the legal system that currently underpins the work of every scientist.

Joseph Stiglitz, winner of a Nobel Memorial Prize in Economic Sciences, has a position largely against strong IP laws. He emphasises that IP seeks to guarantee profits by freezing development and making sure there is no competition. He gives the example of Myriad Genetics, a company that claimed IP on human genes. This is an extreme example, but his observations are widely applicable. He explains that in this case:

Genetic researchers have argued that the patent actually prevented the development of better tests, and so interfered with the advancement of science. All knowledge is based on prior knowledge, and by making prior knowledge less available, innovation is impeded.

Scientists are at the centre of this process, yet they seem oblivious to it. Indeed, if you talk to scientists, as I do (since I am one of them), these issues almost never come up. Ask them about the nature of scientific progress, the funding decisions of their project, the forces behind it or the interests it serves, and you will get a confused look. This is a problem.

Scientists cannot claim neutrality. What if Jonas Salk had decided to work for a pharmaceutical company? Consider a relevant question for the future: if a vaccine for malaria or AIDS is discovered, should it be IP protected to allow monopoly pricing maximising revenue but not health outcomes? More generally: can scientists really justify the predictable outcomes of the projects they are involved in?

What is to be done, then, to maximise the benefit of science from a public perspective? For a start, we can educate scientists and demand more of them. Scientists often participate in outreach events that aim to educate "the public" and explain what they do. In this model the public is merely a recipient vessel which has to understand the decisions made by scientists and research institutions.

But there is no reason this education should be one-directional. Ethics and politics are conspicuously absent of science curricula. It is legitimate and necessary to ask scientists and academics to justify themselves and their use of funding and institutions to the public.

If we rightly scrutinise the actions of private companies or money being spent on social programs and get to debate political priorities in the public sphere, why would scientific research decisions and working models be exempt from scrutiny?

We scientists should be able to seriously address fundamental questions about our work: what sectors of society does a particular research agenda serve? What agents, public and private, are expected to benefit from anticipated discoveries? What sectors of society might be harmed by them? What could be the misuses of those discoveries? And these answers should go beyond superficial observations used to justify funding.

Scientists often do not have a clear view of the wider impact of their research or think about the forces that shape it.

As I have illustrated, the results of their progress have serious consequences. Science is an incredibly powerful force that consumes a vast amount of resources, and those who make this machine run need to make sure it's running in a good direction.

http://phys.org/news/2014-03-antarctic-moss-years-ice.html#rssowlmlink

Antarctic moss lives after 1,500 years under ice

Researchers from the British Antarctic Survey and University of Reading report in Current Biology on March 17 that Antarctic mosses can essentially come back to life after 1,500 completely inactive years under the ice.

Prior to this finding, direct regeneration from frozen plant material had been demonstrated after 20 years at most. Beyond that, only microbes had been shown to be capable of revival after so many years on hold.

"These mosses were basically in a very long-term deep freeze," says Peter Convey of the British Antarctic Survey. "This timescale of survival and recovery is much, much longer than anything reported for them before."

The findings in mosses have special relevance for Antarctic ecosystems and climate, Convey adds, because mosses are primary producers on land in both northern and southern polar regions. In the north in particular, mosses are responsible for storing most of the fixed carbon. If mosses can survive in this way for such long periods of time, then regrowth once the ice retreats wouldn't require long-distance, transoceanic colonization events.

Convey and his colleagues primarily study polar moss cores because they provide a novel archive of past climate conditions. The researchers use them to assess growth rates over time and as proxies to reconstruct aspects of the environment and environmental change over time. The oldest moss banks of the type under study in the Antarctic date back 5,000 to 6,000 years. The one the researchers focused on in the current work is nearly 2,000 years old at its base.

In the beginning, the researchers weren't sure that mosses frozen for more than a decade or two would remain viable. When they began to see the 1,500-year-old mosses start to regrow, it came as a real surprise.

As it happened, getting them to grow didn't even take any coaxing. "We actually did very little other than slice the moss core very carefully," Convey says, adding that they also make sure not to accidentally get any other life forms in the mix. They placed the sliced and seemingly lifeless mosses in an incubator environment at a normal growth temperature and light level, and voila, new shoots of the parent species began to appear.

While 1,500 years on ice is impressive to say the least, the findings suggest that it may be possible for mosses to persist for even longer.

"The potential clearly exists for much longer survival—although viability between successive interglacials would require a period of at least tens of thousands of years," the researchers write. "Such a possibility provides an entirely new survival mechanism and a refugium for a major element of the polar terrestrial biota."

More information: Current Biology, Roads et al.: "Millennial timescale regeneration in a moss from Antarctica." dx.doi.org/10.1016/j.cub.2014.01.053

http://www.eurekalert.org/pub_releases/2014-03/uoc-ner031414.php#rssowlmlink

New evidence raises questions about the link between fatty acids and heart disease

A new study raises questions about current guidelines which generally restrict the consumption of saturated fats and encourage consumption of polyunsaturated fats to prevent heart disease.

The research was published today, 18 March, in the journal Annals of Internal Medicine.

An international research collaboration led by the University of Cambridge analysed existing cohort studies and randomised trials on coronary risk and fatty acid intake. They showed that current evidence does not support guidelines which restrict the consumption of saturated fats in order to prevent heart disease. The researchers also found insufficient support for guidelines which advocate the high consumption of polyunsaturated fats (such as omega 3 and omega 6) to reduce the risk of coronary disease.

Furthermore, when specific fatty acid subtypes (such as different types of omega 3) were examined, the effects of the fatty acids on cardiovascular risk varied even within the same broad 'family' – questioning the existing dietary guidelines that focus principally on the total amount of fat from saturated or unsaturated rather than the food sources of the fatty acid subtypes.

Dr Rajiv Chowdhury, the lead author of the research at the University of Cambridge, said: "These are interesting results that potentially stimulate new lines of scientific inquiry and encourage careful reappraisal of our current nutritional guidelines. "Cardiovascular disease, in which the principal manifestation is coronary heart disease, remains the single leading cause of death and disability worldwide. In 2008, more than 17 million people died from a cardiovascular cause globally. With so many affected by this illness, it is critical to have appropriate prevention guidelines which are informed by the best available scientific evidence."

For the meta-analysis, the researchers analysed data from 72 unique studies with over 600,000 participants from 18 nations. The investigators found that total saturated fatty acid, whether measured in the diet or in the bloodstream as a biomarker, was not associated with coronary disease risk in the observational studies. Similarly, when analysing the studies that involved assessments of the consumption of total monounsaturated

fatty acids, long-chain omega-3 and omega-6 polyunsaturated fatty acids, there were no significant associations between consumption and cardiovascular risk.
Interestingly, the investigators found that different subtypes of circulating long-chain omega-3 and omega-6 fatty acids had different associations with coronary risk, with some evidence that circulating levels of eicosapentaenoic and docosahexaenoic acids (two main types of long-chain omega-3 polyunsaturated fatty acids), and arachidonic acid (an omega-6 fat) are each associated with lower coronary risk.
Similarly, within saturated fatty acid, the researchers found weak positive associations between circulating palmitic and stearic acids (found largely in palm oil and animal fats, respectively) and cardiovascular disease, whereas circulating margaric acid (a dairy fat) significantly reduced the risk of cardiovascular disease.
Additionally, when the authors investigated the effects of omega-3 and omega-6 fatty acid supplementations on reducing coronary disease in the randomised controlled trials, they did not find any significant effects – indicating a lack of benefit from these nutrients.
Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation, which helped fund the study, said: "This analysis of existing data suggests there isn't enough evidence to say that a diet rich in polyunsaturated fats but low in saturated fats reduces the risk of cardiovascular disease. But large scale clinical studies are needed, as these researchers recommend, before making a conclusive judgement.
"Alongside taking any necessary medication, the best way to stay heart healthy is to stop smoking, stay active, and ensure our whole diet is healthy – and this means considering not only the fats in our diet but also our intake of salt, sugar and fruit and vegetables."

http://www.eurekalert.org/pub_releases/2014-03/gumc-pad031314.php#rssowlmlink

Primary androgen deprivation therapy ineffective for most men with early prostate cancer

A study of more than 15,000 men with early stage prostate cancer finds that those who received androgen deprivation as their primary treatment instead of surgery or radiation did not live any longer than those who received no treatment.

WASHINGTON - The research team, led by scientists at Georgetown Lombardi Comprehensive Cancer Center, say that the risks of serious adverse events associated with the treatment — which has been linked to impaired cognition, heart disease, diabetes and other disorders — "mitigates against any clinical or policy rationale for use of primary androgen deprivation therapy in these men."
The findings, reported Monday in the Journal of Clinical Oncology, draw from cancer registries linked with extensive electronic medical records in three, large integrated health plans. The men included in the study had prostate cancer that had not spread beyond the organ (localized) and did not have surgery or radiation therapy, considered curative treatment.
Androgen deprivation therapy suppresses the production of testosterone, the male hormone said to fuel growth of prostate cancer. The therapy improves survival when given with radiation for later stages of disease, and is considered the standard of care for men who have metastatic prostate cancer. Effectiveness of primary androgen deprivation therapy (PADT) has not been established.
"This study is the most comprehensive study on the effectiveness of PADT for men who forgo radiation and surgery for their localized prostate cancer, and it tells us there is no strong reason to use it in most patients," says the study's lead investigator, Arnold Potosky, PhD, a professor of oncology and director of health services research at Georgetown Lombardi. "We found only a small survival benefit for primary androgen deprivation therapy compared to no therapy in men diagnosed with higher-risk localized prostate cancer."
Use of primary androgen deprivation therapy for early stage prostate cancer is widespread. Despite the lack of randomized clinical trials to test its effectiveness, recent studies have reported it as the second most common treatment, after radiotherapy, for clinically localized prostate cancer among older men age 65 and older. The study did not compare androgen deprivation therapy directly to either surgery or radiation therapy, the two main curative treatment options for prostate cancer.
While the study did not probe the reasons why physicians prescribe the treatment in this setting, it was much more common in older men and those with higher risk of disease progression. Potosky speculates that men and their doctors may feel the treatment is a useful option to delay progression of prostate cancer for men who are not good candidates for, or who prefer to avoid, surgery or radiation due to their side-effects.
"Primary androgen deprivation therapy may be preferable to some men with early stage prostate cancer who would prefer to do something rather than watch and wait for further signs of progression to occur later and then need treatments," Potosky adds. "However, using PADT by itself immediately after diagnosis in the hopes of limiting cancer's progression does not extend survival, according to this study."

The researchers are now using their database of 15,170 patients to examine rates of potential side effects from the treatment. "Given the aging American population, more men are likely to be faced with prostate cancer so its is very important to understand the whether the risks of primary androgen deprivation therapy outweigh the survival benefit," he says. "Ultimately, this is a decision for men and their doctors to make together, and we hope that our study provides some helpful information to guide these decisions."

Researchers from Kaiser Permanente Southern California, Kaiser Permanente Northern California, Henry Ford Hospital, Boston University School of Public Health, Harvard Medical School, Massachusetts General Hospital and the Neiman Health Policy Institute participated in the study.

The authors report having no personal financial interests related to the study.

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http://www.eurekalert.org/pub_releases/2014-03/tl-tlc031414.php#rssowlmlink

The Lancet: China halves tuberculosis prevalence in just 20 years

Over the last 20 years, China has more than halved its tuberculosis (TB) prevalence, with rates falling from 170 to 59 per 100 000 population.

This unrivalled success has been driven by a massive scale-up of the directly observed, short-course (DOTS) strategy, from half the population in the 1990s to the entire country after 2000, according to findings from a 20-year-long analysis of national survey data, published in The Lancet.

"One of the key global TB targets set by the Stop TB Partnership aims to reduce tuberculosis prevalence by 50% between 1990 and 2015. This study in China is the first to show the feasibility of achieving such a target, and China achieved this 5 years earlier than the target date", says study leader Dr Yu Wang from the Chinese Center for Disease Control and Prevention in Beijing, China.

"Huge improvements in TB treatment, driven by a major shift in treatment from hospitals to local public health centres implementing the DOTS strategy, were largely responsible for this success."*

China is a major contributor to the TB pandemic, with 1 million new TB cases every year, accounting for 11% of all new cases globally. Two national surveys of tuberculosis prevalence in 1990 and 2000 showed that levels of TB were reduced by around 30% in the 13 provinces where the DOTS programme was adopted. However, national TB prevalence fell by just 19% over the decade.

Another survey was done in 2010 to re-evaluate the national TB burden, providing an opportunity to assess the effect of the nationwide expansion of the DOTS programme. Nearly 253 000 individuals aged 15 years and older were surveyed in 2010 at 176 investigation points chosen from all 31 mainland provinces. The results show that between 2000 and 2010, national TB prevalence fell by 57%—tripling the reduction of the previous decade.

During this time, 87% of the total decrease in prevalence was among cases already diagnosed with TB before the survey. The increase of known TB cases treated using DOTS rose from 15% in 2000 to 66% in 2010, and contributed to lower proportions of treatment default (from 43% to 22%) and retreatment (from 84% to 31%).

According to the authors, "The DOTS programme has been much more effective in reducing the prevalence of tuberculosis in known cases than in new cases. Because the prevalence in known cases is already very low, future reduction in tuberculosis prevalence is likely to slow substantially unless control efforts in addition to the DOTS strategy are implemented, especially in earlier case detection and treatment and use of new instruments."

Writing in a linked Comment, Giovanni Battista, Director of the WHO Collaborating Centre for Tuberculosis and Lung Diseases in Italy, and Giovanni Sotgiu from the University of Sassari-Research in Italy, point out that because many developing countries have already improved TB treatment using the DOTS strategy, "Long-term, rapid reduction in the tuberculosis burden leading to tuberculosis elimination will need additional efforts, including adoption of new instruments in diagnosis (rapid molecular testing for drug-susceptible and drug-resistant tuberculosis) and treatment (new drugs effective against drug-resistant cases), systematic diagnosis and treatment of latent tuberculosis infection, and better access to care by high-risk populations (including free diagnosis and treatment, and social protection mechanisms preventing income loss)."

http://www.wired.com/wiredscience/2014/03/rootworm-resistance-bt-corn/#rssowlmlink

Voracious Worm Evolves to Eat Biotech Corn Engineered to Kill It

One of agricultural biotechnology's great success stories may become a cautionary tale of how short-sighted mismanagement can squander the benefits of genetic modification.

By Brandon Keim

After years of predicting it would happen - and after years of having their suggestions largely ignored by companies, farmers and regulators - scientists have documented the rapid evolution of corn rootworms that are resistant to Bt corn. Until Bt corn was genetically altered to be poisonous to the pests, rootworms used to cause billions of dollars in damage to U.S. crops. Named for the pesticidal toxin-producing Bacillus thuringiensis

gene it contains, Bt corn now accounts for three-quarters of the U.S. corn crop. The vulnerability of this corn could be disastrous for farmers and the environment.

“Unless management practices change, it’s only going to get worse,” said Aaron Gassmann, an Iowa State University entomologist and co-author of a March 17 Proceedings of the National Academy of Sciences study describing rootworm resistance. “There needs to be a fundamental change in how the technology is used.”

First planted in 1996, Bt corn quickly became hugely popular among U.S. farmers. Within a few years, populations of rootworms and corn borers, another common corn pest, had plummeted across the midwest. Yields rose and farmers reduced their use of conventional insecticides that cause more ecological damage than the Bt toxin.

By the turn of the millennium, however, scientists who study the evolution of insecticide resistance were warning of imminent problems. Any rootworm that could survive Bt exposures would have a wide-open field in which to reproduce; unless the crop was carefully managed, resistance would quickly emerge.

Key to effective management, said the scientists, were refuges set aside and planted with non-Bt corn. Within these fields, rootworms would remain susceptible to the Bt toxin. By mating with any Bt-resistant worms that chanced to evolve in neighboring fields, they’d prevent resistance from building up in the gene pool.

But the scientists’ own recommendations — an advisory panel convened in 2002 by the EPA suggested that a full 50 percent of each corn farmer’s fields be devoted to these non-Bt refuges — were resisted by seed companies and eventually the EPA itself, which set voluntary refuge guidelines at between 5 and 20 percent. Many farmers didn’t even follow those recommendations.

Fast forward to 2009, when Gassmann responded to reports of extensive rootworm damage in Bt cornfields in northeast Iowa. Populations there had become resistant to one of the three Bt corn varieties. (Each variety produces a different type of Bt toxin.) He described that resistance in a 2011 study; around the same time, reports of rootworm-damaged Bt corn came in from parts of Illinois, Minnesota, Nebraska and South Dakota. These didn’t represent a single outbreak, but rather the emergence, again and again, of resistance.

'A widespread increase in trait failure maybe just around the corner.'

In the new paper, Gassmann describes further incidents of Bt resistance in other parts of Iowa. He also found rootworms resistant to a second variety of Bt corn. Moreover, being resistant to one variety heightened the chances of resistance to another. That means corn engineered to produce multiple Bt toxins — so-called stacked varieties — won’t do much to slow the evolution of rootworm resistance, as was originally hoped.

Farmers likely won’t stop using Bt corn, as it’s still effective against other pests — but as rootworms become more resistant, said Gassmann, farmers will turn to insecticides, thus increasing their costs and losing the ecological benefits originally gained by using Bt corn. As entomologists concerned by rootworm resistance wrote to the EPA in 2012, “When insecticides overlay transgenic technology, the economic and environmental advantages of rootworm--protected corn quickly disappear.”

Entomologist Bruce Tabashnik of the University of Arizona called Bt resistance “an increasingly serious problem,” and said that refuge sizes need to be increased dramatically and immediately. He and other scientists have pushed the EPA to double current refuge requirements, but so far without success. “Biotech companies have successfully lobbied EPA for major reductions in refuge requirements,” said Tabashnik.

Entomologist Elson Shields of Cornell University agrees. “Resistance was caused because the farmers did not plant the required refuges and the companies did not enforce the planting of refuges,” said Shields, who has written that “a widespread increase in trait failure may be just around the corner.”

In addition to increasing refuge sizes, farmers also need to vary the crops planted on their fields, rather than planting corn season after season, said Gassmann. Breaks in the corn cycle naturally disrupt rootworm populations, but the approach fell from favor as the high price of corn made continuous planting appealing. “Continuous corn is the perfect habitat for rootworm,” said Gassmann.

Shields also lamented the difficulty he and other academic scientists long experienced when trying to study Bt corn. Until 2010, after organized objections by entomologists at major agricultural universities forced seed companies to allow outside researchers to study Bt corn, the crop was largely off-limits. Had that not been the case, said Shields, resistance could have been detected even earlier, and perhaps stalled before it threatened to become such a problem.

“Once we had legal access, resistance was documented in a year,” Shields said. “We were seeing failures earlier but were not allowed to test for resistance.”

There’s a lesson to be learned for future crop traits, Shields said. Rootworm resistance was expected from the outset, but the Bt seed industry, seeking to maximize short-term profits, ignored outside scientists. The next pest-fighting trait “will fall under the same pressure,” said Shields, “and the insect will win. Always bet on the insect if there is not a smart deployment of the trait.”

http://phys.org/news/2014-03-chicken-bones-true-story-pacific.html#rssowlmlink

Chicken bones tell true story of Pacific migration

Did the Polynesians beat Columbus to South America? Not according to the tale of migration uncovered by analysis of ancient DNA from chicken bones recovered in archaeological digs across the Pacific.

Phys.org - The ancient DNA has been used to study the origins and dispersal of ancestral Polynesian chickens, reconstructing the early migrations of people and the animals they carried with them.

The study, led by the University of Adelaide's Australian Centre for Ancient DNA (ACAD) and published today in Proceedings of the National Academy of Sciences, reveals that previous claims of contact between early Polynesians and South America were probably based on contaminated results. Instead, the new study has identified and traced a unique genetic marker of the original Polynesian chickens that is only present in the Pacific and Island Southeast Asia.

The research team of national and international collaborators, including Australian National University, University of Sydney, and Durham and Aberdeen Universities in the UK, used female-inherited mitochondrial DNA extracted from chicken bones excavated in archaeological digs from islands including Hawaii, Rapa Nui (Easter Island) and Niue.

"We have identified genetic signatures of the original Polynesian chickens, and used these to track early movements and trading patterns across the Pacific," says lead author Dr Vicki Thomson of ACAD. "We were also able to trace the origins of these lineages back into the Philippines, providing clues about the source of the original Polynesian chicken populations."

Associate Professor Jeremy Austin, ACAD Deputy Director, says: "There are still many theories about where the early human colonists of the remote Pacific came from, which routes they followed and whether they made contact with the South American mainland. Domestic animals, such as chickens, carried on these early voyages have left behind a genetic record that can solve some of these long standing mysteries."

Project leader Professor Alan Cooper, Director of ACAD says: "We were able to re-examine bones used in previous studies that had linked ancient Pacific and South American chickens, suggesting early human contact, and found that some of the results were contaminated with modern chicken DNA, which occurs at trace levels in many laboratory components," says ACAD Director Professor Alan Cooper. "We were able to show that the ancient chicken DNA provided no evidence of any pre-Columbian contact between these areas."

"Remarkably, our study also shows that the original Polynesian lineages appear to have survived on some isolated Pacific islands, despite the introduction of European domestic animals across the Pacific in the last couple of hundred years," Professor Cooper says. "These original lineages could be of considerable importance to the poultry industry which is concerned about the lack of genetic diversity in commercial stocks."

http://nyti.ms/PKn70Z

A Tumor, the Embryo's Evil Twin

During her first encounter with cancer, Susan Sontag described a tumor as a "demonic pregnancy." "This lump is alive," she wrote in "Illness as Metaphor," "a fetus with its own will."

George Johnson RAW DATA

She could hardly know that the comparison would become more than a figure of speech.

Since the book was published in 1978, scientists have been finding that the same genes that guide fetal cells as they multiply, migrate and create a newborn child are also among the primary drivers of cancer. Once the baby is born, the genes step back and take on other roles. But through decades of random mutations, old embryological memories can be awakened and distorted. What is born this time is a tumor.

"Cancer proceeds by a science-fiction scenario," Sontag wrote, invoking movies like "Invasion of the Body Snatchers" and "The Blob." When Ridley Scott's "Alien" appeared at the cinema in 1979, his imaginary space creatures, hatching their eggs inside human bodies, made her comparisons seem all the more gruesome.

There is no need, of course, for an alien impregnation. Cancer can be provoked by a carcinogen or a hormonal imbalance — or just a senseless, spontaneous mutation. Tipped from its equilibrium, a cell begins multiplying faster than it should. Two cells become four, then eight, then 16. Sontag's demonic pregnancy, like "Rosemary's Baby," stirs to life.

Rough similarities between the growth of a tumor and the gestation of an embryo were first suggested more than a century ago. But no one could have guessed that the parallels would turn out to be so precise.

Consider the gene SHH. The name is short for sonic hedgehog. (Hedgehog genes were discovered in fruit flies and when mutated they cause the larvae to be covered with a profusion of bristles.) In a human embryo, sonic hedgehog is involved with establishing the bilateral symmetry of the brain, skeleton and other organs. Later in

life it can run amok, interacting with genes like SMO (for smoothened — another fruit fly derivation) to bring on a human brain cancer called medulloblastoma and a skin cancer called basal cell carcinoma.
Step by step, these and other genes play powerful roles in both creating and subverting a human life. In the early days of pregnancy, the primitive embryo — this rapidly dividing glob of cells — eats out a spot in the uterine lining using corrosive enzymes called proteases. Then it holds tight for the duration with the help of proteins like integrin, a kind of biological glue. Both types of molecules are also used by a cancer as it digs in and adheres to its berth.
Whether confronted by a tumor or a healthy pregnancy, the immune system reacts with alarm. To keep from being rejected like a mismatched organ transplant, the budding embryo sends chemical signals to quell the counterattack. Cancer cells engage in the same subterfuge.
As the embryo becomes established it secretes other enzymes, and these lead to the sprouting of blood vessels — a nourishing connection to the mother's circulatory system. This process, called angiogenesis, is also exploited by a tumor as it fuels its growth by creating its own parasitic blood supply.
After hooking into the bloodstream, cancer seeds can spread to other parts of the body and sprout new malignancies. The process, called metastasis, appears to be driven by the same mechanism used in the embryo to dispatch freshly created cells to their proper locations.
In this complex metamorphosis, epithelial cells — the kind that stick together in sheets to form bodily tissues — are converted into loosely organized cells called mesenchyme. In this state they are free to move where they are needed to make body parts. Once they arrive they can regroup to form tissues and organs.
In a healthy embryo, this is an orderly affair. In cancer it leads not to new organs but to more tumors.
There is a point where cancer parts ways with its legacy from embryogenesis. Crucial to the development of a fetus is a phenomenon called apoptosis. The name, derived from ancient Greek, refers to the falling away of leaves from a tree or petals from a flower. Another name for it is cellular suicide.
In the burgeoning of cells that occurs during gestation, many are superfluous, and apoptosis encourages them to die. From a weblike flipper, distinguishable fingers emerge like sculpture from rock.
Once the new being is pushed into the world, apoptosis continues to be involved. Normal cells know to die when they become badly deranged. But an aspiring cancer soon learns how to wire around the self-destruct button. Spinning further out of control, it goes on to produce the mockery of a fetus called a tumor.
Confronted by the roiling chemical confusion inside a living cell, metaphors — the comparison of the strange to the familiar — can help scientists focus, separating signals from noise. But they can also beguile and mislead.
Sontag's aim in her book was to explore how the language we invent for illness reflects society's own diseases — its fairy-tale attitudes toward death, its addiction to unrestrained growth, consumption and violence.
Though she didn't say so in the book, her own treatment for breast cancer involved a radical mastectomy and intense chemical warfare to stop the invader. In an optimistic moment she hoped that clinical advances would lead to a softening of the militaristic imagery as gentler therapies were developed, ones that stimulate the body's own natural defenses.
Her enthusiasm was premature. Immune system therapy is recently showing renewed signs of promise. But when Sontag was given, later in life, a diagnosis of a cancer of the uterus and then — the one that killed her in 2004 — a cancer of the blood, the old warlike treatments remained the norm. For all the advances in understanding what cancer is like on a cellular level, that is still the reality today.

http://nyti.ms/1olzRH2

His Fertility Advance Draws Ire

Shoukhrat Mitalipov's Mitochrondrial Manipulations

By Sabrina Tavernise

Beaverton, Ore. — To most people, the word "mitochondria" is only dimly familiar, the answer to a test question in some bygone high-school biology class. But to Shoukhrat Mitalipov, the mysterious power producers inside every human cell are a lifelong obsession.
"My colleagues, they say I'm a 'mitochondriac,' that I only see this one thing," he said recently in his modest, clutter-free office at Oregon Health and Science University. He smiled. "Maybe they are right."
With a name that most Americans can't pronounce (it is Shoe-KHRAHT Mee-tuhl-EE-pov) and an accent that sounds like the villain's in a James Bond film, Dr. Mitalipov, 52, has shaken the field of genetics by perfecting a version of the world's tiniest surgery: removing the nucleus from a human egg and placing it into another. In doing so, this Soviet-born scientist has drawn the ire of bioethicists and the scrutiny of federal regulators.
The procedure is intended to help women conceive children without passing on genetic defects in their cellular mitochondria. Such mutations are rare, but they can cause severe problems, including neurological damage,

heart failure and blindness. About one in 4,000 babies in the United States is born with an inherited mitochondrial disease; there is no treatment, and few live into adulthood.

Mitochondria have their own sets of genes, inherited solely from mothers, and women who carry mitochondrial mutations are understandably eager to not pass them to their children. Dr. Mitalipov's procedure would allow these women to bear children by placing the nucleus from the mother's egg into a donor egg whose nucleus has been removed. The defective mitochondria, which float outside the nucleus in the egg's cytoplasm, are left behind. "It was a major breakthrough," said Douglas C. Wallace, a professor of pathology and laboratory medicine at the University of Pennsylvania. "He's an exceptionally talented person."

But the resulting baby would carry genetic material from three parents — the mother, the host egg's donor and the father — an outcome that ethicists have deplored.

That specter drew critics from all over the country to a hotel in suburban Maryland late last month, where Dr. Mitalipov tried to persuade a panel of experts convened by the Food and Drug Administration that the procedure, which he has pioneered in monkeys, was ready to test in people.

Some told the officials that the technique could introduce new genetic mutations into the human gene pool. Others warned that it could be used later for something ethically murkier — perhaps, said Marcy Darnovsky, executive director of the Center for Genetics and Society, "to engineer children with specific character traits."

Back in his office, Dr. Mitalipov waved off those warnings. Mitochondrial DNA comprises just 37 genes, which direct the production of enzymes and molecules that the cell needs for energy, he noted. They have nothing to do with traits like eye and hair color, which are encoded in the nucleus.

"There are always people trying to stir things up," said Dr. Mitalipov, an American citizen who grew up in what is now Kazakhstan. "Many of them made their careers by criticizing me."

The United States is not the only country weighing mitochondrial replacement. In Britain, the government has issued draft regulations that would govern clinical trials in people. If accepted into law by Parliament, such trials, which are how banned, would be allowed to go forward, although regulators would have to license any clinical application.

Dr. Mitalipov's fixation on mitochondria began in graduate school in Russia in the 1990s. After graduating from an agricultural institute — and a brief, unhappy stint as a manager on a collective farm — he began work on his doctoral thesis at the Research Center of Medical Genetics, a prestigious state-funded institution in Moscow. He focused on embryonic stem cells, which can be grown in the laboratory and turned into any type of cell in the body.

He noticed a strange thing. When stem cells were extracted from a mouse embryo and put in a petri dish, they stopped aging but remained healthy and growing, as if frozen in time. Somewhere in the cell, it seemed, was a clock that determined its life span.

The search for the clock took him to Utah State University for postdoctoral research in the mid-1990s. He developed an interest in cloning, a process in which the cellular clock is not only stopped but reset. Why, he wondered, do cloned animals have normal life spans?

The answer to the riddle of cellular aging was not to be found in the cell's nucleus, Dr. Mitalipov concluded, but in the surrounding cytoplasm. In the mitochondria. "Everything was falling into place in my head," he said.

As researchers began to suspect defective mitochondria as a cause in more diseases, Dr. Mitalipov wondered whether replacing them might be possible.

Scientists already had experimented with combining genetic material from three people to make a baby. About 15 years ago, researchers in New Jersey injected a bit of cell fluid from donor eggs into the eggs of women who were having fertility problems. Those experiments, which came shortly after the cloning of Dolly the sheep, set off such a uproar that the F.D.A. eventually told researchers that they could not perform them without special permission.

Dr. Mitalipov persevered. At Oregon Health and Science University's National Primate Research Center, one of eight in the country, he spent years perfecting a way to create monkey eggs with donated mitochondria. He persuaded software developers to adapt a program that would allow real-time viewing of the necessary microsurgery. A special microscope was developed so that human hands, too blunt an instrument on their own, could conduct the operation with joysticks that look like upside-down flashlights.

"He's just a really practical guy," said Daniel M. Dorsa, senior vice president for research at the university. "He just nose-to-the-grindstone plowed through and figured out what it took."

Success came in 2008 in a darkened, hot laboratory room. On April 24, 2009, twin male rhesus monkeys, Mito and Tracker, were born with replaced mitochondria. Later, with some adjustments Dr. Mitalipov replicated the procedure in human eggs. Because of federal rules against genetic manipulation, the eggs were not allowed to

mature. His research has brought persistent criticism. “If these procedures are carried out, it crosses a very bright line,” said Ms. Darnovsky of the genetics center.
She said that the current goal, mitochondrial replacement, may be narrow, but that Dr. Mitalipov’s genetic techniques could lead to broader applications and eventually to a situation in which scientists or governments “compete to enhance future generations,” such as producing soldiers who never need sleep.
Sheldon Krimsky, a bioethicist who attended the F.D.A. meeting on behalf of the Council for Responsible Genetics, argues that mitochondrial replacement is simply unnecessary. There are other options for women with mitochondrial defects to have healthy children, such as getting an egg from a donor, or having prenatal genetic diagnosis to find eggs with fewer mutations, he said.
“There’s that genetic chauvinism that says unless my DNA is in the child, it will not be truly my child,” he said.
Would-be parents, on the other hand, have been following Dr. Mitalipov’s work with the intensity of the hungry waiting for food. When he came back from the meeting in Maryland, his inbox contained an avalanche of emails from women with mitochondrial mutations and other fertility problems.
Dr. Dorsa said the university still has not decided whether to formally ask the F.D.A. for permission to move forward with clinical trials.
Dr. Mitalipov, for his part, is determined.
“We are ready now to move on to the next stage,” he said. “Not in 10 years, but in the next few years.”

http://www.wired.com/wiredscience/2014/03/narwhal-tusks-enormous-sensory-organs/#rssowlmlink

The Narwhal’s Tusk Is Filled With Nerves. But Why?

For centuries, the purpose of a narwhal’s tusk has eluded explanation.

By Nadia Drake

Narwhals' long tusks are sensory organs capable of detecting changes in seawater concentration. **Glenn Williams, outside Pond Inlet**

Now, researchers suggest that these small whales use their tusks as sensory organs and speculate that sensing changes in seawater salinity might help male narwhals stay safe, and locate fish or females.
Narwhals are a little bit like Arctic unicorns. At least, the males are. They’re the beasts that swim around wielding giant, spiraling tusks that can grow to nearly 9 feet long. But unlike the mythical horned horse, narwhals are a) real and b) their horns aren’t centered on their faces. Instead, their tusks protrude from the left of their mouths – they’re actually big, twisted canine teeth (the right canine usually remains embedded in the whale’s jaw).
Since at least the 15th century, scientists have been mulling over the purpose of the narwhal’s super-long tooth, proposing roles in defense, attracting a mate, hunting, hearing, breathing, and ice-breaking, among others. Now, it seems clear that the tooth is capable of acting like an enormous sensory organ, says Harvard University’s Martin Nweeia, a marine mammal dental specialist. Nweeia and his colleagues have been studying narwhals in the Arctic for more than a decade, and published a paper describing the tooth’s sensory capabilities today in The Anatomical Record.
“It takes a tremendous amount of energy and devotion to get that thing to grow,” Nweeia says. “To expend that much energy in such a harsh environment – there has to be a pretty compelling reason to do it.”
Nweeia and his colleagues collected narwhal tusks from Inuit hunters near Baffin Island, then studied those tusks for anatomical clues to their function. Turns out, narwhal tusks are filled with a nerve-rich pulp that’s similar to the stuff in human teeth that can sometimes make drinking coffee or eating ice cream a painful experience.
Next, the team looked to see if there were any genes expressed by the pulp that would indicate a role in relaying sensory information to the brain. And there were: two genes expressed in sensory signaling pathways were present at much higher levels in tusk pulp than in muscle or jaw tissues.
Nweeia then decided to test whether the tusks helped convey information about salt concentration in the surrounding sea. To do this, he fitted narwhals with a “tusk jacket” – a clear plastic tube that encloses the tusk, from one end to the other. He attached electrodes to the animals so that he could measure their heart rate. Then he bathed the jacketed tusks in solutions with either high or low concentrations of dissolved salt – a situation that mimics changes to seawater as icebergs form (high salt) or melt (low salt).
He found that narwhal heart rates rose in response to high salt concentrations, presumably because these concentrations normally suggest that the sea is freezing and entrapment is possible. The animals’ heart rates dropped when the tusks were washed with fresh water, suggesting they could detect this change. But, Nweeia

says, salt is just one of many environmental stimuli the tusks could be sensing. “Our premise was just to open the pathway for people understand that this is a sensory organ,” he says. “Now the pathway is open for people, including ourselves, to look at other variables it might also detect.”

http://www.eurekalert.org/pub_releases/2014-03/uons-lim031614.php#rssowlmlink

Less is more: New theory on why very low nutrient diets can extend lifespan

UNSW scientists have developed a new evolutionary theory on why consuming a diet that is very low in nutrients extends lifespan in laboratory animals - research that could hold clues to promoting healthier ageing in humans.

Scientists have known for decades that severely restricted food intake reduces the incidence of diseases of old age, such as cancer, and increases lifespan. "This effect has been demonstrated in laboratories around the world, in species ranging from yeast to flies to mice. There is also some evidence that it occurs in primates," says lead author, Dr Margo Adler, an evolutionary biologist at UNSW Australia.

The most widely accepted theory is that this effect evolved to improve survival during times of famine. "But we think that lifespan extension from dietary restriction is more likely to be a laboratory artefact," says Dr Adler.

Her study with UNSW's Associate Professor Russell Bonduriansky, is published in the journal BioEssays.

Lifespan extension is unlikely to occur in the wild, because dietary restriction compromises the immune system's ability to fight off disease and reduces the muscle strength necessary to flee a predator.

"Unlike in the benign conditions of the lab, most animals in the wild are killed young by parasites or predators," says Dr Adler. "Since dietary restriction appears to extend lifespan in the lab by reducing old-age diseases, it is unlikely to have the same effect on wild animals, which generally don't live long enough to be affected by cancer and other late-life pathologies." Dietary restriction, however, also leads to increased rates of cellular recycling and repair mechanisms in the body.

The UNSW researchers' new theory is that this effect evolved to help animals continue to reproduce when food is scarce; they require less food to survive because stored nutrients in the cells can be recycled and reused.

It is this effect that could account for the increased lifespan of laboratory animals on very low nutrient diets, because increased cellular recycling reduces deterioration and the risk of cancer.

"This is the most intriguing aspect, from a human health stand point. Although extended lifespan may simply be a side effect of dietary restriction, a better understanding of these cellular recycling mechanisms that drive the effect may hold the promise of longer, healthier lives for humans," Dr Adler says.

It may be possible in future, for example, to develop drugs that mimic this effect.

Video abstract: http://www.youtube.com/watch?v=KG2Etkr8Hek

http://news.discovery.com/animals/sea-anemone-animal-and-plant-in-one-140318.htm#mkcpgn=rssnws1

Sea Anemone Is Both Animal and Plant

Sea anemones are classified as being animals, but two new genetic studies have found that these water-dwelling creatures are technically half plant and half animal.

Mar 18, 2014 10:00 AM ET // by Jennifer Viegas

The discovery does not change the classification of sea anemones, but the studies -- both published in the latest issue of the journal Genome Research -- reveal just how interconnected life on Earth is.

"All animals living now, including humans, are equally distant (i.e. distantly related) to plants," project leader Ulrich Technau told Discovery News. "However, the sea anemones are representatives of an animal lineage called the cnidarians (corals, sea anemones, jellyfish and hydras), which branched off very early and appear to have retained many ancestral traits." Technau, an evolutionary and developmental biologist at the University of Vienna, and his teams determined that, remarkably, cnidarians use a plant-like system to control animal genes.

Striped colonial anemones are shown. The creatures have been revealed to be part animal, part plant. **Nhobgood, Wikimedia Commons**

For the studies, the researchers focused on gene expression, which is the process by which information from a gene is used in the synthesis of a functional gene product, such as proteins or large biological molecules known as RNA. Gene expression involves at least two main steps: transcription and translation. Transcription is the process of making an RNA copy of a gene sequence. Translation is the process of translating the sequence of a messenger RNA molecule to a sequence of amino acids during protein synthesis.

The scientists determined that regulation of transcription for sea anemones is comparable to that for other animals. On the other hand, the second level of regulation for sea anemones, translation, is much more plant-

like. "Since sea anemones have branched off very early, we assume that they have retained this plant-like mode from a common ancestor, hence, in terms of the regulation of gene expression, they are somewhat mixed," Technau said.

Two-Thirds Marine Species Remain Unknown

The basic animal aspects of gene expression, which we share with them, evolved a very long time ago. Co-author Michaela Schwaiger explained, "Since the sea anemone shows a complex landscape of gene regulatory elements similar to the fruit fly or other model animals, we believe that this principle of complex gene regulation was already present in the common ancestor of human, fly and sea anemone some 600 million years ago."

While sea anemones branched off, still retaining some of their plant-like ways, the common ancestor of insects and vertebrates (including mammals, birds, reptiles, amphibians and fishes) either lost these genetic ways of plants, or drastically modified them. Technau suspects that the common ancestor of sea anemones, humans and flies was "a simple-looking pear or worm-shaped" creature with a basic nervous system, an oral opening and a gut.

David Miller of James Cook University's Coral Genomics Group described the papers as "very elegant and thorough." "Cnidarians appear to use a plant-like system to regulate typical animal genes, many of which are shared between the sea anemone and you and me. How cool is that?" Miller said.

As Technau concluded, "Maybe it is worth trying to learn something from organisms that have managed to survive over 600 million years."

http://www.eurekalert.org/pub_releases/2014-03/acs-tpr022414.php#rssowlmlink

The precise reason for the health benefits of dark chocolate: Mystery solved

The health benefits of eating dark chocolate have been extolled for centuries, but the exact reason has remained a mystery -– until now.

DALLAS - Researchers reported here today that certain bacteria in the stomach gobble the chocolate and ferment it into anti-inflammatory compounds that are good for the heart.

Their findings were unveiled at the 247th National Meeting & Exposition of the American Chemical Society (ACS), the world's largest scientific society. The meeting, attended by thousands of scientists, features more than 10,000 reports on new advances in science and other topics. It is being held at the Dallas Convention Center and area hotels through Thursday. "We found that there are two kinds of microbes in the gut: the 'good' ones and the 'bad' ones," explained Maria Moore, an undergraduate student and one of the study's researchers. "The good microbes, such as Bifidobacterium and lactic acid bacteria, feast on chocolate," she said. "When you eat dark chocolate, they grow and ferment it, producing compounds that are anti-inflammatory." The other bacteria in the gut are associated with inflammation and can cause gas, bloating, diarrhea and constipation. These include some Clostridia and some E. coli.

"When these compounds are absorbed by the body, they lessen the inflammation of cardiovascular tissue, reducing the long-term risk of stroke," said John Finley, Ph.D., who led the work. He said that this study is the first to look at the effects of dark chocolate on the various types of bacteria in the stomach. The researchers are with Louisiana State University.

The team tested three cocoa powders using a model digestive tract, comprised of a series of modified test tubes, to simulate normal digestion. They then subjected the non-digestible materials to anaerobic fermentation using human fecal bacteria, according to Finley.

He explained that cocoa powder, an ingredient in chocolate, contains several polyphenolic, or antioxidant, compounds such as catechin and epicatechin, and a small amount of dietary fiber. Both components are poorly digested and absorbed, but when they reach the colon, the desirable microbes take over. "In our study we found that the fiber is fermented and the large polyphenolic polymers are metabolized to smaller molecules, which are more easily absorbed. These smaller polymers exhibit anti-inflammatory activity," he said.

Finley also noted that combining the fiber in cocoa with prebiotics is likely to improve a person's overall health and help convert polyphenolics in the stomach into anti-inflammatory compounds. "When you ingest prebiotics, the beneficial gut microbial population increases and outcompetes any undesirable microbes in the gut, like those that cause stomach problems," he added. Prebiotics are carbohydrates found in foods like raw garlic and cooked whole wheat flour that humans can't digest but that good bacteria like to eat. This food for your gut's helpful inhabitants also comes in dietary supplements.

Finley said that people could experience even more health benefits when dark chocolate is combined with solid fruits like pomegranates and acai. Looking to the future, he said that the next step would be for industry to do just that.

This study was supported by the Louisiana State College of Agriculture and a Louisiana AgCenter Undergraduate Research Grant.

Impact of the microbiome on cocoa polyphenolic compounds

Abstract

Flavanols such as catechin, epicatechin and polymers are abundant in cocoa products, however their fate in the lower gastrointestinal tract is not clear. We investigated the impact of the human gut microbiome on three different types of cocoa powders: lavado, Geekins Sienna, and Paragon. The cocoa powders differed in sources and processing methods. The materials were predigested in a gastrointestinal model and the non-digestible residues were anaerobically fermented in a human gastrointestinal model. Short chain fatty acids, changes in pH and phenolic profiles were determined at 0, 6, 12, 18 and 24 hours. Fatty acid production was compared to hi-Maize Resistant Starch (positive control). The pH dropped slightly between 6 and 12 hours and acetic acid, butyric acid, and propionic acid were found. The phenolic profiles suggested breakdown of larger molecules to simpler phenolic acids. Colonic fermentation may be responsible for some of the benefits of coca products.

http://www.eurekalert.org/pub_releases/2014-03/sumc-foe031314.php#rssowlmlink

Form of epilepsy in sea lions similar to that in humans, Stanford researchers find

California sea lions exposed to a toxin in algae develop a form of epilepsy that is similar to one in humans, according to a new study led by Stanford University School of Medicine researchers.

STANFORD, Calif. -Every year, hundreds of sea lions wash up along the California coast, suffering seizures caused by exposure to domoic acid, a neurotoxin that can produce memory loss, tremors, convulsions and death. Domoic acid is produced by algae blooms that have been proliferating along the coast in recent years, accumulating in anchovies and other small fish that the sea lions feed on, said Paul Buckmaster, PhD, DVM, professor of comparative medicine at Stanford.

Buckmaster and his colleagues studied the brains of affected sea lions and found they had a pattern of damage in the hippocampus — the brain's memory center — much like that in humans with temporal lobe epilepsy. "We found there was a loss of neurons in specific patterns that closely matched what is found in people," he said. "And there is synaptic reorganization — a rewiring of surviving neurons. This also matches what is found in humans with temporal lobe epilepsy." He said further studies in the animals could help in developing better treatments for them, as well as for their human counterparts. Buckmaster is lead author of the study, which will be published online March 19 in the Journal of Comparative Neurology.

Temporal lobe epilepsy is one of the most common forms of epilepsy in humans and has no cure. It typically begins with a seizure caused by an insult to the brain, such as head trauma, high fever or lack of oxygen. Months or years later, it progresses into epilepsy, with periodic seizures that may be treated with anti-convulsive medication or, in some cases, surgery.

There is one documented case of a patient who was found to have developed temporal lobe epilepsy following exposure to domoic acid. The 84-year-old Canadian was one of more 250 people who became ill in 1987 after eating mussels from Prince Edward Island that were found to be contaminated with domoic acid. The man, who suffered nausea, vomiting, coma and convulsions, initially recovered but was diagnosed a year later with temporal lobe epilepsy; he died some two years later of pneumonia. Three other Canadians died in the mussel incident as a result of domoic acid poisoning.

In sea lions, the first link between domoic acid and epilepsy was established in 1998, when some 400 animals washed ashore in California's Monterey Bay on Memorial Day weekend. Some had died, while others were in the throes of seizures, weaving their heads, flailing about and scratching themselves in an odd way. About 100 of the animals were rescued by the Marine Mammal Center in Sausalito, where experts were at a loss to explain the animals' bizarre behavior, said Frances Gulland, PhD, DVM, senior scientist at the center and co-author of the current study.

She contacted Christopher Scholin, PhD, now president of the Monterey Bay Aquarium Research Institute, who discovered the bay waters had the highest levels of domoic acid ever recorded, she said. Blood and urine samples from the sea lions confirmed they had domoic acid poisoning. The researchers documented their findings in a 2000 Nature paper.

Since then, Gulland said a few hundred sea lions with epilepsy have been rescued every year by the mammal center, and about half respond to treatment with anti-convulsive therapy. But some suffer from seizures that may continue for hours, causing extensive brain damage. These animals have no hope for recovery and have to be euthanized. In these cases, mammal center officials turn to Buckmaster, a veterinarian who is an expert in epilepsy in animals. For the past four years, he has been working on studies of the epileptic sea lions, examining samples of their brain tissue to better understand what underlies the disease.

In the current study, he and his colleagues retrieved samples of tissue from the hippocampus, which they cut into thin slices and then stained so that the neurons could be viewed under a microscope. They collected tissues

from 14 sea lions with epilepsy and compared them with similar samples from nine without epilepsy who had died of other causes, such as cancer, infection or shark bite wounds.

The animals with epilepsy had lost about 50 percent of the neurons in the hippocampus, similar to what is seen in people with temporal lobe epilepsy, Buckmaster said. The researchers observed another striking similarity: In most cases, the hippocampus on only one side of the brain in the sea lions showed any signs of damage.

"That was really surprising," Buckmaster said. "That is what you find in people — 80 percent of the time the damage is just on one side." In rats and mice, which are the models typically used in epilepsy studies, injury is seen in the hippocampus of both sides of the brain, he said. The results are curious, as sea lions ingest the toxin throughout their bodies, he said. "Why would there be damage only on one side?"

He speculated that it could be related to the size and structure of the brain. Like the human brain, the sea lion brain is significantly larger than a rodent brain — 700 times larger than a mouse brain and 180 times larger than a rat brain — and contains many more neurons. However, the average number of synapses — connections between nerve cells — per neuron is roughly the same in rodents and humans. Without more synapses for each neuron, the probability of any two neurons in the large brain being connected must be lower than it is in the small brain, Buckmaster surmised. So this relative lack of interconnectivity in human and sea lion brains could be why damage remains localized to a specific area, he said. (The number of synapses hasn't been measured in sea lions, though it seems reasonable to speculate that they would have a similar ratio of synapses per neuron, he said.)

The researchers also noticed a pattern of rewiring in the brains of the epileptic sea lions that is similar to that in humans with temporal lobe epilepsy. Among the neurons that survived the assault by domoic acid, some of the axons — the nerve fibers that carry electrical impulses away from the neuron — extended into a region of the hippocampus where they don't normally grow. That creates a kind of positive feedback loop in which the cells are exciting themselves, which might contribute to more seizure activity, Buckmaster said.

"We see this in people with temporal lobe epilepsy," he said. "It's one of the key neuropathological features of the disease."

Because of these similarities, he said the sea lions could serve as good models for developing new treatments for the disease. Patients typically are treated with daily, anti-convulsive drugs, or in some cases with surgery in which doctors remove a portion of the hippocampus — an invasive procedure that often causes some memory loss. The ultimate goal, he said, is to develop a therapy that could be used early on to forestall brain damage and prevent further seizures. "What we need is an interventional treatment — both in humans and sea lions," he said. "You'd give the treatment right after the brain injury, and that would prevent them from developing epilepsy. That's the dream, but we are not there yet."

Gulland said the research has been a valuable contribution to the field. "For us, the work Dr. Buckmaster has done is really important because it shows the sea lions are really epileptic," she said. "We used to think if they had just a small amount of the poison, they could recover and be fine. But if the seizure has gone on for any length of time, they become permanently affected. It's very distressing to the animals and to the people who work with them to see them coming back having seizure after seizure."

Buckmaster is now planning new studies of the sea lions using the entire brain, fully preserved right after the animals' death so the "beautiful anatomy" of various structures is visible. "We will be able to see areas of brain damage we have never seen before," he said. "Based on the hippocampus results, there's a good chance it will be similar to people."

He also has a grant to study the effects of in utero exposure to domoic acid. Some of the sea lions in the study were younger animals thought to be exposed before birth, as domoic acid can concentrate in amniotic fluid at a time when the nervous system is developing, Buckmaster said. The mammal center has treated three pups from mothers that were exposed to domoic acid in pregnancy, two of whom developed epilepsy later in life. It's believed that humans could be susceptible to in utero damage from the toxin as well, he said.

Meanwhile, the problem of marine mammal exposure to domoic acid is not likely to go away anytime soon. The harmful algae blooms, believed to be produced by micronutrients contained in agricultural runoff, have been increasing in frequency along the California coast and are lasting longer, sometimes for months at a time, Gulland said.

And while sea lions may be the most visible victims, it's believed that other marine mammals, such as whales and dolphins, are affected by the toxin and may have seizures and drown in the open ocean, though the extent of the problem isn't known, Gulland said. William van Bonn, DVM, formerly of the Marine Mammal Center and now at the Shedd Aquarium in Chicago, was senior author of the paper.

Other Stanford co-authors were research assistant Xiling Wen, MD, and graduate student Izumi Toyoda, DVM.
The study was supported by the National Institutes of Health (grant R01ES021960) and the National Science Foundation.

http://www.eurekalert.org/pub_releases/2014-03/cwru-ubd031814.php#rssowlmlink

Using big data to identify triple-negative breast, oropharyngeal, and lung cancers

Researchers at Case Western Reserve University and colleagues used "big data" analytics to predict if a patient is suffering from aggressive triple-negative breast cancer, slower-moving cancers or non-cancerous lesions with 95 percent accuracy.

If the tiny patterns they found in magnetic resonance images prove consistent in further studies, the technique may enable doctors to use an MRI scan to diagnose more aggressive cancers earlier and fast track these patients for therapy. Their work is published online in the journal Radiology at http://pubs.rsna.org/doi/full/10.1148/radiol.14131384.

The work comes just two months after senior author Anant Madabhushi and another group of researchers showed they can detect differences between persistent and treatable forms of head and neck cancers caused by exposure to human papillomavirus, with 87.5 percent accuracy. In that study, digital images were made from slides of patients' tumors. Next up, Madabhushi's lab recently received a $534,000, 2-year grant from the Department of Defense to find the patterns of indolent versus aggressive cancer in the lungs. The goal is to diagnose the presence of aggressive lung cancers from CT scans alone.

"Literally, what we're trying to do is squeeze out the information we're not able to see just by looking at an image," said Madabhushi, a professor of biomedical engineering at Case School of Engineering and director of the Center for Computational Imaging and Personalized Diagnostics.

Searching for telltale markers

Madabhushi worked with Shannon C. Agner at Rutgers University and Mark A. Rosen, MD; Sarah Englander; Mitchell D. Schnall, MD; Michael D. Feldman, MD; Paul Zhang, MD; and Carolyn Miles; MD, at the University of Pennsylvania, on the breast cancer study. They analyzed MR images of breast lesions from 65 women. The researchers sifted through hundreds of gigabytes of image data from each patient to try to find differences that distinguish the different subtypes of breast cancers from each other.

Madabhushi and his colleagues discovered that triple-negative cancer, benign fibroadenoma that is commonly mistaken for triple-negative, and two other common types of breast cancer—estrogen-receptor positive (ER+) and human epidermal growth factor receptor type 2-postive (HER2+)—reflect different textures when images are enhanced with contrasting agents.

The scientists mathematically modeled the textures that appear as the tissues absorb contrast-enhancing dye. The model revealed that changes over just milliseconds distinguished triple-negative from benign lesions. The investigators used machine learning and pattern recognition methods to aid in diagnoses among the three types of cancers based on texture changes and other quantitative evidence.

"Today, if a woman or her doctor finds a lump, she gets a mammogram and then a biopsy for molecular analysis, which can take two weeks or up to a month," Madabhushi said. "If we can predict the cancer is triple-negative, we can fast track the patient for biopsy and treatment. Especially in cases with triple-negative cancer, two to four weeks saved can be crucial." For the three types of cancers, the early diagnosis would enable quick and personalized treatments. ER+ and HER2+ respond to different therapies. An MRI could also become a regular screening device for women who have family histories of these cancers.

Other cancers

Using much the same science, Madabhushi and fellow researchers from Washington University developed a way to distinguish between recurrent and treatable forms of a specific head and neck cancer called human papillomavirus-related oropharyngeal squamous cell carcinoma. That work was published earlier this year in the American Journal of Surgical Pathology. The abstract can be found at http://www.ncbi.nlm.nih.gov/pubmed/24145650. "Most sufferers tend to have good outcomes, but a small subset—about 10 percent—doesn't," he said. "There's nothing out there to predict which. "We developed an algorithm and found patterns that allowed us to distinguish between the two with 80 to 90 percent accuracy."

After scanning biopsy and tumor resection slides from 160 patients into a computer, the researchers found they could use nuclei of the cancerous cells to characterize and measure cell distribution and clustering patterns. They found where the nuclei of cells had reverted to a more primitive form, a condition called anaplasia, the cells were tightly clustered and the patient suffered recurrent cancer. They graphed the nuclei in each of the images and found there was little to no overlap between the highly clustered recurrent cancer and the comparatively disperse treatable form.

The results, if confirmed through further studies, could lead to milder treatment for patients who have the non-recurrent cancer and more aggressive treatment for those with recurrent cancer, the researchers say.

"Personalized medicine is possible using this," Madabhushi said. "Using biopsy specimens, pathologists can't tell one from the other, but big data analytics can." His lab's newest project is to find characteristics that can identify cancer or precancerous conditions in the lungs, and distinguish among different types of lung cancers. The majority of lung cancers are diagnosed at advanced stages, beyond the period in which surgery can be successful. Survival rate for one of the worst forms, non small-cell lung cancer, remains at 15 to 18 percent. In this study, the lab will use x-ray images taken with computed tomography scans to build their digital image library.

The other researchers on the lung cancer study are Philip Linden, MD, associate professor of surgery; Robert Gilkeson, MD, professor of radiology; Frank Jacono, MD, associate professor of medicine; and Michael Yang, MD, assistant professor of pathology, at the Case Western Reserve School of Medicine; and postdoctoral associates Mirabela Rusu and Mahdi Orooji from the Madabhushi lab.

On the oropharyngeal cancer study, Madabhushi worked with Sahirzeeshan Ali, a Case Western Reserve PhD student in electrical engineering and computer science, and James Lewis Jr., MD; Lingquin Luo; and Wade L. Thorstad, MD; from Washington University.

http://www.eurekalert.org/pub_releases/2014-03/uab-sey031814.php#rssowlmlink

Strongest evidence yet of 2 distinct human cognitive systems

Cognitive scientists able to isolate implicit from explicit learning processes

BUFFALO. N.Y. — Cognitive scientists may have produced the strongest evidence yet that humans have separate and distinct cognitive systems with which they can categorize, classify, and conceptualize their worlds.

"Our finding that there are distinct, discrete systems has implications for the fields of child development and cognitive aging," says lead researcher, cognitive psychologist J. David Smith, PhD, of the University at Buffalo.

"These distinct systems may have different developmental courses as the cortex matures," he says, "meaning that children may categorize differently than adults, using different systems at different ages. This would have educational and training implications in cases of developmental disability."

He says the systems also may have different courses of decline in cognitive aging, which would have ramifications for remediation and compensation in dementia.

The study "Deferred Feedback Sharply Dissociates Implicit and Explicit Category Learning," was conducted by Smith and colleagues at UB and at the University of California at Santa Barbara. It was published in the Feb. 7 edition of the journal Psychological Science.

The age-old question of whether humans have discrete cognitive systems operating on different levels that are more or less conscious, more or less available to introspection, and so forth, has been debated for years.

"This issue of whether there are separate cognitive systems famously arose regarding humans' declarative and procedural memory and in the field of categorization," Smith says. "Cognitive neuroscientists have hypothesized that humans have distinguishable systems for categorizing the objects in their world — one more explicit (i.e., conscious and available to introspection), one less so, or more implicit," says Smith.

To grasp the differences between these two types of learning, Smith recommends that we remember certain distinctions in our performance of the tasks of daily life.

"For instance, when you select a cereal named 'Chocoholic' from the store shelf," he says, "consider why you are doing so. Is it a deliberate, explicit choice, or is it possibly an implicit-procedural chocolate reaction, one triggered by processes, memories and so on, of which you are generally unaware?"

"Because of the considerable controversy surrounding the question of whether we have more than one cognitive system, researchers have continued to seek models that distinguish the processes of explicit and implicit category learning," Smith says, "and this study presents the clearest distinction yet found between these systems.

"To make this discovery," he says, "we borrowed an influential model from our studies of macaque monkeys, which illustrates the valuable synergies that exist between primate and human research."

Their technique was to ask humans to work for blocks of trials without any corrective feedback, and then deliver feedback when they were finished. Smith likens this process to an undergraduate testing situation in which the student taking a test does not get item-by-item feedback, but receives a summary score once the test is completed.

Because this manipulation, he says, prevents the formation of automatic (implicit) stimulus-response associations, Smith and his colleagues hypothesized that it would undermine the processes of conditioning and eliminate the possibility of implicit category learning. "Implicit category learning," he says, "is a system that depends on trial-by-trial feedback of response correctness and incorrectness to establish the stimulus-response associations that allow implicit learning and responding.

"In fact," Smith says, "the blocked-feedback technique made implicit category learning impossible. We then used extensive trial-strategy analyses and formal-mathematical modeling to demonstrate this conclusively.

"So we were able to selectively unplug one category-learning system — the implicit system — but leave the explicit-conscious system functioning and intact," he says.
Smith et al. even found that, facing a task that could only be learned implicitly, participants with blocked feedback turned futilely to conscious strategies that were inadequate, because this was all they could do when implicit category learning was defeated.
"In the area of categorization research," Smith says, "the issue of single vs. multiple systems is nearly closed. The evidence is now very strong that there are multiple category-learning systems — in particular, the explicit-conscious and the implicit-procedural system."
Smith says it is fascinating to consider where in cognitive evolution the roots of the explicit-declarative categorization system lie. He and his colleagues have found the beginnings of this system in non-human primates like rhesus macaques and capuchin monkeys. Interestingly, though, thus far pigeons have shown no evidence of having distinguishable explicit and implicit systems.
Smith's co-authors were Joseph Boomer and Alexandria C. Zakrzewski, graduate students, andBarbara Church PhD, senior research scientist, all in the UB Department of Psychology, and graduate student Jessica Roeder and F. Gregory Ashby, PhD, both in the Department of Psychological and Brain Sciences, University of California, Santa Barbara.

http://www.eurekalert.org/pub_releases/2014-03/uops-scf031714.php#rssowlmlink

Stem cells from muscle can repair nerve damage after injury, Pitt researchers show

Stem cells derived from human muscle tissue were able to repair nerve damage and restore function in an animal model of sciatic nerve injury, according to researchers at the University of Pittsburgh School of Medicine.

PITTSBURGH - The findings, published online today in the Journal of Clinical Investigation, suggest that cell therapy of certain nerve diseases, such as multiple sclerosis, might one day be feasible.
To date, treatments for damage to peripheral nerves, which are the nerves outside the brain and spinal cord, have not been very successful, often leaving patients with impaired muscle control and sensation, pain and decreased function, said senior author Johnny Huard, Ph.D., professor of orthopaedic surgery, and Henry J. Mankin Chair in Orthopaedic Surgery Research, Pitt School of Medicine, and deputy director for cellular therapy, McGowan Institute for Regenerative Medicine.
"This study indicates that placing adult, human muscle-derived stem cells at the site of peripheral nerve injury can help heal the lesion," Dr. Huard said. "The stem cells were able to make non-neuronal support cells to promote regeneration of the damaged nerve fiber."
The researchers, led by Dr. Huard and Mitra Lavasani, Ph.D., first author and assistant professor of orthopaedic surgery, Pitt School of Medicine, cultured human muscle-derived stem/progenitor cells in a growth medium suitable for nerve cells. They found that, with prompting from specific nerve-growth factors, the stem cells could differentiate into neurons and glial support cells, including Schwann cells that form the myelin sheath around the axons of neurons to improve conduction of nerve impulses.
In mouse studies, the researchers injected human muscle-derived stem/progenitor cells into a quarter-inch defect they surgically created in the right sciatic nerve, which controls right leg movement. Six weeks later, the nerve had fully regenerated in stem-cell treated mice, while the untreated group had limited nerve regrowth and functionality. Twelve weeks later, treated mice were able to keep their treated and untreated legs balanced at the same level while being held vertically by their tails. When the treated mice ran through a special maze, analyses of their paw prints showed eventual restoration of gait. Treated and untreated mice experienced muscle atrophy, or loss, after nerve injury, but only the stem cell-treated animals had regained normal muscle mass by 72 weeks post-surgery.
"Even 12 weeks after the injury, the regenerated sciatic nerve looked and behaved like a normal nerve," Dr. Lavasani said. "This approach has great potential for not only acute nerve injury, but also conditions of chronic damage, such as diabetic neuropathy and multiple sclerosis."
Drs. Huard and Lavasani and the team are now trying to understand how the human muscle-derived stem/progenitor cells triggered injury repair, as well as developing delivery systems, such as gels, that could hold the cells in place at larger injury sites.
Co-authors of the paper include Seth D. Thompson, B.S., Jonathan B. Pollett, Ph.D., Arvydas Usas, M.D., Aiping Lu, M.D., Donna B. Stolz, Ph.D., Katherine A. Clark, B.S., Bin Sun, Ph.D., and Bruno Péault, Ph.D., all of the University of Pittsburgh.
The project was funded by National Institutes of Health grants AR049684 and NS081724-01, the U.S. Department of Defense, the Henry J. Mankin Endowed Chair for Orthopaedic Research at the University of Pittsburgh, the William F. and Jean W. Donaldson Chair at Children's Hospital of Pittsburgh of UPMC, the Hirtzel Foundation, and the Pittsburgh Claude Pepper Older Americans Independence Center.

http://www.bbc.com/news/science-environment-26172181##rssowlmlink

Ancient Earth hammered by double space impact

We've all seen the films where an asteroid hurtles towards our planet, threatening civilisation. What's less well known is that menacing space rocks sometimes come in twos.

By Paul Rincon Science editor, BBC News website, The Woodlands, Texas

Researchers have outlined some of the best evidence yet for a double space impact, where an asteroid and its moon apparently struck Earth in tandem. Using tiny, plankton-like fossils, they established that neighbouring craters in Sweden are the same age - 458 million years old. Details of the work were presented at the 45th Lunar and Planetary Science Conference in The Woodlands, Texas, and the findings are to be published in the Meteoritics and Planetary Science journal. However, other scientists cautioned that seemingly contemporary craters could have landed weeks, months or even years apart.

A handful of possible double impacts (or doublets) are already known on Earth, but Dr Jens Ormo says there are disputes over the precision of dates assigned to these craters. "Double impact craters must be of the same age, otherwise they could just be two craters right next to each other," the researcher from the Centre for Astrobiology in Madrid, Spain, told BBC News. Dr Ormo and his colleagues studied two craters called Lockne and Malingen, which lie about 16km apart in northern Sweden. Measuring about 7.5km wide, Lockne is the bigger of the two structures; Malingen, which lies to the south-west, is about 10 times smaller.

Binary asteroids are thought to form when a so-called "rubble pile" asteroid begins to spin so fast under the influence of sunlight that loose rock is thrown out from the object's equator to form a small moon. Telescope observations suggest that about 15% of near-Earth asteroids are binaries, but the percentage of impact craters on Earth is likely to be smaller.

Proposed double impact craters
Clearwater East and West (Canada): 26km/36km diameter, 290 million years old
Kamensk and Gusev (Russia): 25km/3km diameter, 49 million years old
Ries and Steinheim (Germany): 25km/3.8km, 14.5 or 15 million years old

Only a fraction of the binaries that strike the Earth will have the necessary separation between the asteroid and its moon to produce separate craters (those that are very close together will carve out overlapping structures). Calculations suggest around 3% of impact craters on Earth should be doublets - a figure that agrees with the number of candidates already identified by researchers.

The unusual geological characteristics of both Lockne and Malingen have been recognised since the first half of the 20th Century. But it took until the mid-1990s for Lockne to be formalised as a terrestrial impact crater.

In the last few years, Dr Ormo has drilled about 145m down into the Malingen structure, through the sediment that fills it, down to crushed rocks known as breccias and deeper, reaching the intact basement rock.

Lab analysis of the breccias revealed the presence of shocked quartz, a form of the quartz mineral that is created under intense pressures and is associated with asteroid strikes.

This area was covered by a shallow sea at the time of the Lockne impact, so marine sediments would have begun to fill in any impact craters immediately after they were created.

One-two punch

Dr Ormo's team set out to date the Malingen structure using tiny fossilised sea creatures called chitinozoans, which are found in sedimentary rocks at the site. Their method, known as biostratigraphy, allows geologists to assign relative ages to rocks based on the types of fossil creatures found within them.

The results revealed the Malingen structure to be the same age as Lockne - about 458 million years old. This seems to confirm that the area was rocked by a double asteroid strike during the Ordovician Period.

Dr Gareth Collins, who studies impact cratering at Imperial College London, and was not involved with the research, told BBC News: "Short of witnessing the impacts, it is impossible to prove that two closely separated craters were formed simultaneously. "But the evidence in this case is very compelling. Their proximity in space and consistent age estimates makes a binary-impact cause likely." Clearwater East and West The Clearwater East and West craters are the best known candidates for a double impact

Simulations suggest the asteroid that created Lockne was some 600m in diameter, while the one that carved out Malingen was about 250m. These measurements are somewhat larger than might be suggested by their craters because of the mechanics of impacts into marine environments.

Dr Ormo added that Malingen and Lockne were just the right distance apart to have been created by a binary. As mentioned, if two space rocks are too close, their craters will overlap. But to qualify as a doublet, the craters can't be too far apart, because they will exceed the maximum distance at which an asteroid and its moon can stay bound by gravitational forces.

"The Lockne impactor was big enough to generate what's known as an atmospheric blow-out, where you blow away the atmosphere above the impact site," said Dr Ormo. This can cause material from the asteroid strike to

spread around the globe, as happened during the huge Chicxulub impact thought to have killed off the dinosaurs 66 million years ago.
The Ordovician event wasn't powerful enough for that material to be traced, as it would have been very dilute in the atmosphere. But the impact would have had regional effects; for example, any sea creatures unlucky enough to be swimming nearby would have been instantly vaporised.
Other candidate double impact craters include Clearwater East and West in Quebec, Canada; Kamensk and Gusev in southern Russia; and Ries and Stenheim in southern Germany.

http://phys.org/news/2014-03-python-homing-stuns-scientists.html#rssowlmlink

Python's homing trick stuns scientists

The Burmese python has a built-in compass that allows it to slither home in a near-straight line even if released dozens of kilometres away, researchers say

The Burmese python has a built-in compass that allows it to slither home in a near-straight line even if released dozens of kilometres away, researchers said Wednesday.
Capable of growing over five metres (16 feet) long, pythons are among the world's largest snakes. Although native to South and Southeast Asia, the snakes have taken up residence in South Florida's Everglades National Park, possibly after being released as unwanted pets. They have adapted so well to their new habitat that they now pose a serious threat to several species which they hunt as prey.
Scientists captured six of the pythons in the Everglades, placed them in sealed, plastic containers, and drove them to locations between 21 and 36 kilometres (13-22 miles) away. They implanted radio trackers in the animals and followed their movements with GPS readings from a small fixed-wing plane—measuring their direction and speed. All the snakes immediately oriented themselves towards the place where they were captured, with five of the six returning to within five kilometres (three miles) of that spot. The sixth veered somewhat off course as it was nearing its destination.
The snakes travelled between 94 and 296 days, displaying "high motivation to reach home locations", according to the study, published in the Royal Society journal Biology Letters.

Keeping track of the python invasion

"This study provides evidence that Burmese pythons have navigational map and compass senses," the authors wrote. No other snake species has yet been shown to possess a similar homing ability.
Such navigational skills suggest the python has a razor-sharp sense of territoriality. This could help combat the species in places where it is unwanted by predicting where the snake is likely to spread.
Burmese pythons eat everything from tiny birds to deer and even alligators. They swallow their food whole.
More information: Homing of invasive Burmese pythons in South Florida: evidence for map and compass senses in snakes,Biol. Lett. March 2014 vol. 10 no. 3 20140040 rsbl.royalsocietypublishing.org/content/10/3/20140040

Abstract

Navigational ability is a critical component of an animal's spatial ecology and may influence the invasive potential of species. Burmese pythons (Python molurus bivittatus) are apex predators invasive to South Florida. We tracked the movements of 12 adult Burmese pythons in Everglades National Park, six of which were translocated 21–36 km from their capture locations. Translocated snakes oriented movement homeward relative to the capture location, and five of six snakes returned to within 5 km of the original capture location. Translocated snakes moved straighter and faster than control snakes and displayed movement path structure indicative of oriented movement. This study provides evidence that Burmese pythons have navigational map and compass senses and has implications for predictions of spatial spread and impacts as well as our understanding of reptile cognitive abilities.

http://www.eurekalert.org/pub_releases/2014-03/wuso-gbc031914.php#rssowlmlink

Gut bacteria can cause life-threatening infections in preterm babies

Babies born prematurely are surviving in increasing numbers. But many withstand complications of early birth only to suffer late-onset sepsis - life-threatening bloodstream infections that strike after infants reach 72 hours of age.

While early-onset sepsis often is caused by pathogens acquired from the amniotic sac or birth canal, the causes of late-onset sepsis have been far less clear. But now, researchers at Washington University School of Medicine in St. Louis have discovered that preterm babies' guts harbor infectious microbes that can cause late-onset sepsis. The research is published March 19 in Clinical Infectious Diseases.
"There is a tremendous emphasis in intensive-care units throughout the world on stopping infections related to the insertion of IVs, catheters or other tubes, but that leaves a sizable subset of people who get bloodstream infections from germs that don't necessarily reside on the skin," said senior author Phillip I. Tarr, MD, the Melvin E. Carnahan Professor of Pediatrics. "It's been suspected that these other infections come from the gut. This research proves that."

The researchers, in collaboration with scientists at Michigan State and the University of Minnesota, found three types of potentially harmful gut microbes in the bloodstreams of most babies in the study who developed late-onset sepsis: E. coli, group B strep and S. marcescens. The findings suggest new strategies to detect and prevent severe bloodstream infections in neonatal intensive care units (NICUs) — and that such strategies include the gut as a target. The findings also are relevant to other patient populations, said study co-author Barbara B. Warner, MD, a professor of pediatrics who treats patients at St. Louis Children's Hospital.

"Although our study was in preterm infants, its applicability is much more broad and may include people who are susceptible to bloodstream infections, for example, people in intensive care units or with chronic illnesses, or cancer patients who take medicine that may suppress their immune systems," Warner said. "Late-onset sepsis is not just a disease in preterm infants — it's a cause of serious illness and death among many acutely ill and immunocompromised patients."

Sepsis, which contributes to billions of dollars in health-care costs each year, occurs when the immune system has an overwhelming response to a bacterial infection. The body releases chemicals into the blood to fight the infection, but this triggers widespread inflammation that can lead to blood clots and leaky blood vessels. In severe cases, sepsis causes shock, organ failure and death.

It's widely accepted that preterm babies - and patients of all ages - can acquire such infections via IVs, catheters and other tubes. These infections are thought to be hospital-based or otherwise associated with health care.

About 20 percent of preterm babies develop late-onset sepsis. Overall, about 10 to 20 percent of infants whose infections aren't successfully treated with antibiotics die because of the condition. This death rate varies according to the bacteria causing sepsis; some gut organisms result in higher death rates, in the range of 20 to 30 percent.

The Washington University investigators, including first author Mike A. Carl, a medical student at Saint Louis University, studied 217 premature infants from whom they collected all stool samples, beginning as soon as possible after birth. The babies had been admitted to the NICU at St. Louis Children's Hospital, which has stringent infection-control practices and sepsis rates that fall below the national average. Still, at or after three days of age, 11 of the infants developed sepsis.

The researchers, working with scientists at The Genome Institute at Washington University School of Medicine, used genome sequencing to compare bacteria in the blood samples of the 11 affected infants with bacteria found in their stool samples, which are a proxy for microbes in the lower intestine, or gut. To assess whether sepsis-causing infections spread between infants, the scientists also compared stool-based bacteria with bacteria in stool samples from two groups of infants without sepsis.

In seven of the 11 infants who developed sepsis, the researchers found that bacteria in stool samples taken days to weeks before the onset of sepsis matched bacteria in the blood samples taken later, suggesting that bacteria from the gut – rather than from other parts of the body – quite likely caused the bloodstream infection.

"We obtained the organism from the blood and then isolated the organism from the stool and then sequenced both," Warner explained. "We could tell, because the sequences were genetically identical, that the source of that organism was the same in the blood as what was in the stool." They also found the same microbes in the stool samples of infants whose NICU stays overlapped, suggesting that such bacteria occasionally are transmitted from infant to infant, though the bacteria don't always lead to illness.

"No one can be completely sterile; it is inevitable that bacteria will be encountered by infants in these settings," said Tarr, who is also a professor of molecular microbiology. "We do not know the origin of these bacteria in most cases. However, this study tells us that at least in a subset of infants who develop bloodstream infections, the germ that invades their blood flourishes in their gastrointestinal tracts for at least a few days before it causes sepsis.

"That's an opportunity to be on top of colonization and to be aggressive in preventing dissemination between infants in NICUs and within infants who are colonized. The concept of sepsis as gut infection offers a new strategy to prevent this serious, hospital-acquired condition independent of assiduous skin care, which we continue to endorse."

Warner stressed that the findings indicate a need to consider infection-control steps outside of those taken regarding the insertion of IVs and other tubes into patients. "We could be spending millions of dollars to decrease line-related sepsis, but health-care and infection-control experts haven't addressed this other *component," she said. "Considering our findings, this should be looked at more broadly and more intensively."*

Carl MA, Ndao M, Springman AC, Manning SD, Johnson JR, Johnston BD, Burnham CD, Weinstock ES, Weinstock GM, Wylie TN, Mitreva M, Abubucker S, Zhou Y, Stevens HJ, Hall-Moore C, Julian S, Shaikh N, Warner BB, Tarr PI. Sepsis from the gut: The enteric habitat of bacteria that cause late-onset neonatal bloodstream infections. Clinical Infectious Diseases. March 19, 2014.

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http://phys.org/news/2014-03-life-primordial-soup.html#rssowlmlink

Can bleach help solve the origin of life in the primordial soup?

A chemical found in hair bleach may help answer questions about the origins of life and explain why new life does not emerge on modern Earth.

Hydrogen peroxide may have helped transform RNA (ribonucleic acid) into one of the building blocks of life, we found in a study published today in Journal of the Royal Society Interface.

More than 3.6 billion years ago there were no living cells and no proteins in the primordial soup on earth.

The RNA world hypothesis holds that cell-free communities grew in rock pores around hydrothermal vents and replicated and evolved, before the evolution of DNA and cell membranes.

But cell-free RNA replication requires thermal cycling – heating to separate the base-paired double strands and a cooling phase to anneal complementary strands into newly replicated double helices.

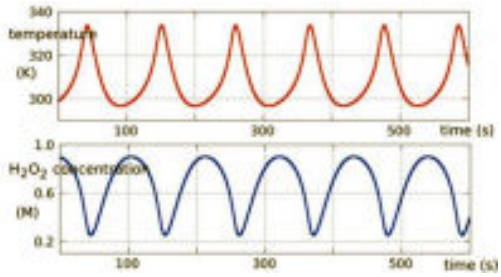
This fact is often overlooked in hypotheses about the origin of life, although the polymerase chain reaction (PCR) method routinely used to amplify DNA in the lab uses artificially imposed thermal cycling.

So what mechanism may have provided spontaneous, self-sustained thermal cycling on the ancient earth?

The breakthrough

Our study brought together interdisciplinary researchers at the Australian National University and Leeds University, UK. Bringing insights gained from applied mathematics and chemical engineering to bear on a problem that has been tackled by chemists and molecular biologists, we described and tested a previously unrecognised mechanism for driving a replicating molecular system on the pre-biotic earth.

Researchers had suggested earlier that thermal cycling may have been provided by convective oscillations in millimetre-sized rock pores.



This is what the hydrogen peroxide thermochemical oscillations look like. The upper plot shows the temperature response, in the lower plot we can see that the hydrogen peroxide concentration oscillates out of phase with the temperature.

We proposed that thermal cycling in the primordial soup may have been provided by a natural thermochemical oscillator, driven by spontaneous, exothermic (heat producing) reactions of hydrogen peroxide.

A thermochemical oscillator is an exothermally reacting chemical system that gives a periodic temperature response. They have been studied experimentally since 1969.

Hydrogen peroxide is a simple molecule with the chemical formula H_2O_2. It is made and used in vast quantities in the polymer industry and has some domestic uses in hair bleach and antiseptics, but it also occurs in small quantities naturally on the Earth and in the biosphere. Oscillatory thermoconversion is typical of highly energetic, thermally sensitive, liquids such as hydrogen peroxide.

Such liquids have high specific heat capacity so their intermolecular bonds can absorb much of the heat of reaction. But when the bonds cannot absorb any more heat the temperature spikes to a maximum, then declines to a minimum, and the cycle begins again.

The hydrogen peroxide oscillator turns out to have just the right period – around 90 seconds – to drive the replication of small RNAs. If the period is too long the RNAs decay faster than replication can increase them. If the period is too short the strands do not separate completely and replication fails.

Replication, amplification and evolution

We set up detailed computational simulations and found that the hydrogen peroxide oscillator can indeed drive rapid RNA replication and amplification. But there's more. In the presence of RNA template strands the oscillatory system can become quasi-periodic, and the thermal oscillations can take on more complex forms – biperiodic, for example. This may lend additional, powerful capabilities to a molecular replicating system. A biperiodic temperature response is capable of replicating two different RNA species, and nature may well have done exactly that in the primordial rock pores.

How might complementary RNA strands have been produced in the pre-biotic primordial soup? Well, it has been shown that long polynucleotides can be synthesised on mineral surfaces. We proposed a surface-promoted scheme, which itself may be driven by the hydrogen peroxide oscillator.

A truly living system must evolve, as well as replicate. Now, RNA is not totally stable in the presence of hydrogen peroxide. This is good, because it allows for some infidelity in replication.
In other words, we also have evolution! RNA that is modified by the action of hydrogen peroxide in such a way that confers resilience to hydrogen peroxide damage would, of course, be selected for. We have natural selection, too!

Other worlds

Experiments have indicated that hydrogen peroxide was present on the early Earth, and may easily have occurred in high enough concentrations to undergo oscillatory thermoconversion in hydrothermal rock pores. Hydrogen peroxide is known also to occur abundantly on Jupiter's moon Europa, and is believed to have occurred formerly on Mars, which suggests that these planetary bodies may have evolved their own RNA worlds!
Our results also may provide an answer to the (previously unanswerable) question of why life does not emerge from non-living precursors on the modern earth. We do not find spontaneously self-replicating and evolving RNA communities around modern hydrothermal vents. The answer? Quite simply there are no longer the amounts of hydrogen peroxide in those environments that were there in the good old days!

http://www.eurekalert.org/pub_releases/2014-03/uop-cta031914.php#rssowlmlink

Chemo-free treatment a possibility for leukemia/lymphoma

Patients with terminal forms of leukaemia and lymphoma who have run out of treatment options could soon benefit from a new drug, which not only puts an end to chemotherapy and has virtually no side effects but also improves a patient's life expectancy and quality of life.

It has been described as a breakthrough in cancer treatment by a leading professor in haematology, who presented the findings of the Phase 1 trial at an international conference in New Orleans in December 2013.
Professor Simon Rule, Consultant Haematologist at Plymouth Hospitals NHS Trust and researcher at Plymouth University Peninsula Schools of Medicine and Dentistry, has led the first worldwide study of its kind into a new class of BTK (Bruton's Tyrosine Kinase) inhibiting drugs at Derriford Hospital in Plymouth, describes it as 'exciting' and 'a transformation' in the treatment for patients with these conditions.
Professor Rule has observed significant improvements in his patients. The first four patients in the world to receive this drug were treated in Plymouth, starting in September 2012. Since then, more than 30 patients worldwide are receiving this treatment, with positive results.
Professor Rule said: "The astonishing thing about these drugs is that they have virtually no side effects, which is unprecedented from my experience. In some patients the effects are immediate. Patients with lots of symptoms, particularly those with lymphoma, will feel better the next day after taking the medication.
"The UK is at the forefront of this drug development and all of the studies into these drugs are being run from Plymouth. This will completely change the way we manage these diseases. We have access to the next generation of the drug to be part of the next trial phases. This is not a cure for cancer but it will mean we are significantly improving our patients' life expectancy and quality of life; similar to managing a chronic condition. I have yet to come across another class of drugs in my career that has been so successful for leukaemia or lymphoma."
Current therapies, such as chemotherapy, intensive chemo-immunotherapy (chemotherapy combined with immunotherapy) or stem cell transplant are effective but due to the aggressive nature of these cancers, patients always relapse and eventually run out of options.
These drugs work by inhibiting Bruton's tyrosine kinase (BTK), a protein which plays a role in the signals that cause growth in cancerous cells. Blocking this causes the cancerous cells to die but normal cells are unaffected. With an average survival rate of four to five years, the new developments in BTK inhibiting drugs could dramatically improve the life expectancy and quality of life for patients with terminal forms of leukaemia and lymphoma who have run out of other treatment options.
David Hodge, 74, from Plymouth, was the first in the world to be treated with this new medication and more than a year on from the start of the trial is feeling the benefits.
Prior to starting the trial in September 2012, David had only several months to live. This was due to his immune system not functioning and also following years of treatment he had become resistant to all other treatments.
Professor Rule continued: "To be brutal, David had no other option. He was resistant to other forms of treatments so I am just pleased to have been able to access this drug and offer it to him."
When asked whether this was the outcome he imagined the trial to have a year ago, Professor Rule said: "I have done a lot of drug trials in my career; this drug and its predecessor, which I was fortunate to be the first person in Europe to use - they are transformational as far as I am concerned.

"So, did I expect this to happen? No, but I was hopeful that this drug would be more effective than similar drugs we could trial.
"Normally what you expect with trials like this is that you treat a patient for a period of time and often what happens is the drug doesn't work; the side effects make you stop the trial or the disease doesn't respond for very long. What is very exciting about this drug is the effects are continuing and there are no emerging side effects."
Professor Rule is now planning to run a UK study from Plymouth using the latest BTK drug in a trial against standard chemotherapy. "The next stage will be chemo-free treatment. We've been talking about it for years and now it might be a reality," he explains. "This has the very real prospect of changing the management of these difficult forms of cancer."
Professor Simon Rule runs the only mantle cell lymphoma clinic in Europe, with one other clinic in America. As a leading clinician in mantle cell lymphoma, patients have come from around the world to seek out Professor Rule's expertise.

David Hodge's Story

David Hodge, 74, from Plymouth, was the first person in the world to be treated with this new medication and 12 months on from the start of the trial is feeling the benefits.
Prior to starting the trial in September 2012, David had only several months to live. This was due to his immune system not functioning and also following years of treatment he had become resistant to all other treatments.
Speaking on the first day of starting to take the BTK drug in September 2012, David explained what it meant to him to be taking part in the trial: "I've had three treatments, one chemo and two other treatments and although I've now had CLL (chronic lymphocytic leukemia), for 17 years, which is remarkable really, of course life is very precious and if my life can be extended I'd give God the thanks for that.
"I think with any new trial or drug, or with chemotherapy there's a little bit of trepidation but I'm a Christian and I prayed about this and I got great peace about it. I just felt, even if it proves at this moment, to be of little use to me; I trust that with 'fine tuning' it will prove to be significant to those taking the drug later on."
On the first night David stayed in hospital and has returned for regular check-ups and telephone calls with the nursing team, who have been on hand 24/7.
Meeting up with him one year on from his treatment and he is doing remarkably well. We asked him how he felt when Professor Rule had said he had a drug for him to try. He told us: "Extremely grateful. Quite frankly, I wasn't as aware, as I am now, how critical my situation was and that this really was the only way out. Had I have known, I would have been more concerned but I am really grateful for this opportunity."
David describes how he's had no problems at all with the drug.
"It's just like, well it's better than taking paracetamol. I take the medication first thing in the morning at 6 'o' clock and then go back to bed for an hour. Afterwards I get up and get on with my day; I'm fighting fit. I've had no problems, no side effects, nothing."
David added: "I'm delighted with Birch Ward and the haematology department here because they really are top professionals, I'm completely confident in what they're doing and I'm quite happy to continue with the trial."

http://www.eurekalert.org/pub_releases/2014-03/snmo-scw031414.php#rssowlmlink

Smithsonian collaborates with paleontologist team to reveal new large, feathered dinosaur

Fossils present first in-depth look at oviraptorosaurs in North America

A team of scientists from the Smithsonian's National Museum of Natural History, the Carnegie Museum of Natural History and the University of Utah has described an unusual bird-like dinosaur previously unknown to science, resembling a cross between a modern emu and a reptile. The new species, Anzu wyliei, lived 68 to 66 million years ago and was identified from three partial skeletons collected from the Upper Cretaceous Hell Creek Formation in North and South Dakota. The species belongs to Oviraptorosauria, a group of dinosaurs mostly known from fossils found in Central and East Asia. The fossils of Anzu provide, for the first time, a detailed picture of the anatomy, biology and evolutionary relationships of North American oviraptorosaurs. A detailed report about the team's research is published by PLOS ONE March 19.
Hans-Dieter Sues, curator of vertebrate paleontology in the Department of Paleobiology at the National Museum of Natural History, and Tyler Lyson, a postdoctoral fellow at the museum, played significant roles in describing and discovering the fossils and participated in the analysis of A. wyliei, recognizing its status as a

new species. Lyson was responsible for the discovery and excavation of one of the three partially complete fossils analyzed by the team; the other two more complete fossils were discovered by private collectors, including Mike Triebold and the Nuss family. All three fossils are now housed at the Carnegie Museum of Natural History in Pittsburgh. Sues and Lyson collaborated with lead author Matthew Lamanna, assistant curator of vertebrate paleontology at the Carnegie Museum of Natural History, and Emma Schachner, a postdoctoral researcher at the University of Utah in Salt Lake City, in describing the new species.
"For almost a hundred years, the presence of oviraptosaurs in North America was only known from a few bits of skeleton, and the details of their appearance and biology remained a mystery," said Sues. "With the discovery of A. wyliei, we finally have the fossil evidence to show what this species looked like and how it is related to other dinosaurs."

Anzu wyliei's Appearance and Biology

The three Anzu specimens preserve almost the entire skeleton of this species, giving scientists their first in-depth look at its striking and unusual anatomy. A. wyliei was roughly 11 feet long and 5 feet tall at the hip. Except for its long tail, it resembled a large flightless bird, with feathers on its arms and tail, a toothless beak and a tall crest on top of its skull. The neck and hind legs were long and slender, similar to those of an ostrich. Unlike in birds, the forelimbs of A. wyliei were tipped with large, sharp claws. The structure of the skull suggests that Anzu may have been an omnivore, and its fossils were found in humid floodplain sediments, like many of the other species excavated from the Hell Creek Formation.
"Over the years, we've noticed that Anzu and some other Hell Creek Formation dinosaurs, such as Triceratops, are often found in mudstone rock that was deposited on ancient floodplains," said Lyson. "Other dinosaurs like duckbills are found in sandstone deposited in or next to rivers."
The fossils of A. wyliei also offer clues about the evolutionary relationships between its family, the Caenagnathidae (pronounced SEE-nuh-NAY-thih-DAY), and the Asian Oviraptoridae. The scientists found that caenagnathids were amazingly diverse, including species that were as small as turkeys and as large as Anzu.
Hell Creek Formation Fossils Highlighted in Upcoming Smithsonian Fossil Exhibition
The National Museum of Natural History will showcase dinosaurs and other fossils from the world in which Anzu lived as part of its upcoming temporary exhibition, "The Last American Dinosaurs: Discovering a Lost World," which opens Nov. 25. The exhibition will feature specimens from the Hell Creek and Lance formations, such as Tyrannosaurus rex and Triceratops. These rock formations date from about 68 to 66 million years ago.
"The Hell Creek Formation has been intensely studied by paleontologists for more than a hundred years, and we're still finding phenomenal specimens," said Kirk Johnson, Sant Director of the National Museum of Natural History. "We are excited and honored to continue sharing our collection of fossil discoveries with our visitors for years to come."
In 2013, the National Museum of Natural History announced a 50-year loan agreement with the U.S. Army Corps of Engineers to transfer a T. rex skeleton to the Smithsonian for eventual display in the museum's new dinosaur hall, scheduled to open in 2019. The skeleton was excavated from the Hell Creek Formation, and it is one of the most complete T. rex specimens ever discovered. The T. rex is set to arrive at the Smithsonian April 15. The last day for the public to visit the current dinosaur hall will be April 27, after which it will close for renovation.

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The Goldilocks principle: New hypothesis explains Earth's continued habitability

Geologic cycles act as a climate control, releasing and absorbing atmospheric carbon dioxide in a balance that helps keep the planet not too hot and not too cold

Researchers from USC and Nanjing University in China have documented evidence suggesting that part of the reason that the Earth has become neither sweltering like Venus nor frigid like Mars lies with a built-in atmospheric carbon dioxide regulator – the geologic cycles that churn up the planet's rocky surface.
Scientists have long known that "fresh" rock pushed to the surface via mountain formation effectively acts as a kind of sponge, soaking up the greenhouse gas CO2. Left unchecked, however, that process would simply deplete atmospheric CO2 levels to a point that would plunge the Earth into an eternal winter within a few million years during the formation of large mountain ranges like the Himalayas – which has clearly not happened.
And while volcanoes have long been pointed to as a source of carbon dioxide, alone they cannot balance out the excess uptake of carbon dioxide by large mountain ranges. Instead, it turns out that "fresh" rock exposed by uplift also emits carbon through a chemical weathering process, which replenishes the atmospheric carbon dioxide at a comparable rate.

"Our presence on Earth is dependent upon this carbon cycle. This is why life is able to survive," said Mark Torres, lead author of a study disclosing the findings that appears in Nature on March 20. Torres, a doctoral fellow at the USC Dornsife College of Letters, Arts and Sciences, and a fellow at the Center for Dark Energy Biosphere Investigations (C-DEBI), collaborated with Joshua West, professor of Earth Sciences at USC Dornsife, and Gaojun Li of Nanjing University in China.
While human-made atmospheric carbon dioxide increases are currently driving significant changes in the Earth's climate, the geologic system has kept things balanced for million of years.
"The Earth is a bit like a big, natural recycler," West said. Torres and West studied rocks taken from the Andes mountain range in Peru and found that weathering processes affecting rocks released far more carbon than previously estimated, which motivated them to consider the global implications of CO2 release during mountain formation.
The researchers noted that rapid erosion in the Andes unearths abundant pyrite — the shiny mineral known as "fool's gold" because of its deceptive appearance — and its chemical breakdown produces acids that release CO2 from other minerals. These observations motivated them to consider the global implications of CO2 release during mountain formation.
Like many other large mountain ranges, such as the great Himalayas, the Andes began to form during the Cenozoic period, which began about 60 million years ago and happened to coincide with a major perturbation in the cycling of atmospheric carbon dioxide. Using marine records of the long-term carbon cycle, Torres, West, and Li reconstructed the balance between CO2 release and uptake caused by the uplift of large mountain ranges and found that the release of CO2 release by rock weathering may have played a large, but thus far unrecognized, role in regulating the concentration of atmospheric carbon dioxide over the last roughly 60 million years.
This research was supported by USC Dornsife College of Letters, Arts, and Sciences and C-DEBI Graduate Fellowships to M.T., NSF funding (NSF-EAR/GLD-1053504 and EAR/GLTG-1227192) to A.J.W., and National Natural Science Foundation of China funding (Grant Nos. 41173105, 91 41102103 and 41321062) to G.L.

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Noninvasive colorectal cancer screening tool shows unprecedented detection rates

Mayo Clinic research results presented in NEJM could change colorectal screening practice

ROCHESTER, Minn. - Results of a clinical trial of Cologuard show unprecedented rates of precancer and cancer detection by a noninvasive test. The detection rates are similar to those reported for colonoscopy. The results were published in the March 20 issue of the New England Journal of Medicine (NEJM). Cologuard was co-developed by Mayo Clinic and Exact Sciences. Cologuard, is a noninvasive sDNA test for the early detection of colorectal precancer and cancer. The Cologuard test is based on a stool sample that is analyzed for DNA signatures of precancer or cancer. The samples are easily collected, mailed from home, requires no bowel preparation, medication restriction or diet change.
The clinical trial, called the DeeP-C study, included 10,000 patients and was designed to determine how well Cologuard detects precancer and cancer. The study also compared Cologuard to the fecal immunochemical test for occult blood (FIT). The study was conducted at 90 medical centers throughout the United States and Canada.
"Cologuard detection rates of early stage cancer and high-risk precancerous polyps validated in this large study were outstanding and have not been achieved by other noninvasive approaches," says the study's author David Ahlquist M.D., a Mayo Clinic gastroenterologist and co-inventor of the Cologuard test. "It is our hope that this accurate and user-friendly test will expand screening effectiveness and help curb colorectal cancer rates in much the same way as regular screening, including genetic testing, has done for cervical cancer."
In the study, all patients received Cologuard, FIT and colonoscopy. Colonoscopy was the reference method. Major findings reported in the study include:

Sensitivity of Cologuard for cancer was 92 percent overall, and 94 percent for the earliest and most curable cancer stages (stages I and II).

Sensitivity was 69 percent for precancerous polyps at greatest risk to progress to cancer (i.e., those containing high-grade dysplasia).

Cologuard detected significantly more cancers and significantly more precancerous polyps than did FIT.

"The most important finding of the study is the high sensitivity of Cologuard for curable stage colorectal cancer, which represents the highest sensitivity of any noninvasive test to date," says Thomas Imperiale, M.D., a Professor of Medicine at Indiana University Medical Center in Indianapolis and a study author. "It is also significant to note that these results were achieved in a robustly conducted multicenter study."
Colorectal cancer is often considered the most preventable, yet least prevented, cancer. Nearly 50 percent of adults age 50 and older have not been screened as recommended and, as a result, colorectal cancer has become

the second-leading cause of cancer death in the United States. Colorectal cancer is highly treatable if found early, and it is preventable if the precancerous polyps at greatest risk of progressing can be detected.
"Dr. Ahlquist's work exemplifies our goal at Mayo Clinic, which is the relentless pursuit of innovation aimed to help our patients. This research will transform how we think about colorectal cancer screening going forward," says Vijay Shah, M.D., chair of Mayo Clinic's Division of Gastroenterology and Hepatology.
Cologuard works by testing a patient's stool for altered DNA shed during digestion. Altered DNA is known to occur within colorectal cancers and precancerous polyps. The test also examines the stool for the presence of blood, another possible indicator of colorectal cancer. Combining the data from the stool DNA test and the blood test into a single result provides a comprehensive, powerful screening approach, which is reflected in the study results.
Because of its accessibility and ease of use, researchers hope the test will increase the number of people who will choose to be screened for colorectal cancer. Screening is important because, if cancer is detected early, removing polyps during a colonoscopy can prevent the cancer.
"This test has the potential to bring colon cancer screening to many patients who might otherwise go without any screening," says Kenneth Wang, M.D., a Mayo Clinic gastroenterologist, director of the Advanced Endoscopy Group and president of the American Society for Gastrointestinal Endoscopy. "I'm hopeful that this will increase the number of patients obtaining lifesaving colonoscopy with early detection and removal of precancerous and early cancerous polyps."
Exact Sciences is the co-developer of Cologuard. The company is in the process of seeking approval from the Food and Drug Administration for the use of Cologuard for colorectal cancer screening. The company is scheduled to appear before the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee on March 27.
The DeepP-C clinical study was funded by Exact Sciences. Mayo Clinic is an equity investor in Exact Sciences. In relation to Exact Sciences, Dr. Ahlquist is a scientific advisor, research collaborator and inventor of licensed technology.

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Inflammation mobilizes tumor cells

Researchers of Ludwig-Maximilians-Universitaet (LMU) in Munich have discovered a novel feedback mechanism that provides a mechanistic link between chronic inflammation and carcinogenesis.

Malignant tumors pose a major threat to survival largely because they shed mobile cells that can form secondary tumors in other tissues. This process requires a fundamental change in the character of cells within the primary tumor, insofar as members of a localized cell mass must be converted into actively migrating cells that invade into the surrounding tissue and blood vessels, and finally settle in distant tissues. A growing body of evidence suggests that inflammatory reactions promote such cellular transformation. The protein interleukin 6 (IL-6) is known to a play a significant role in inflammatory signalling. IL-6 is a cytokine, a signal molecule that is produced and secreted both by immune cells and by tumor cells and binds specifically to a receptor (IL-6R) that is found on the surfaces of many cell types. "As we have now shown, even brief exposure to IL-6 can lead to long-lasting alterations in colon cancer cells that enhance their mobility and thus increase their metastasizing potential," says Heiko Hermeking of LMU's Institute of Pathology.

Short RNA strands repress metastasis

Hermeking and his colleagues set out to discover the functional basis for this effect of IL-6. Using cell cultures derived from colon carcinomas, they found that IL-6 is part of a feedback loop, which also includes a short RNA, microRNA-34a (miR-34a). It turns out that miR-34a plays a central role in repressing the production of tumor-promoting proteins, and thereby normally serves to inhibit tumorigenesis and metastasis. But as Hermeking explains, "Activation of IL-6R upon binding of IL-6 essentially disables this inhibitory mechanism. It does so by activating the transcription factor STAT3, which in turn inhibits expression of the miR-34a gene by directly binding to it." As the Hermeking lab could show, expression of the IL-6 receptor is itself directly repressed by miR-34a. Therefore, loss of the microRNA leads to overproduction of the cytokine receptor. Taken together, IL-6R and miRNA-34a form a feedback loop and depending on whether miR-34a or IL-6 is present in excess, tumor-promoting genes are either repressed or activated.

The feedback loop operates in vivo

Inflammation is associated with increased secretion of IL-6. The newly characterized signal mechanism that acts between IL-6R and miR-34a via STAT3 therefore provides a functional link that helps explain how chronic inflammation facilitates the formation of metastases. "We have demonstrated the significance of this link in a mouse model system, based on the use of a miR-34a-deficient mouse strain that we had generated. In a collaboration with Professor Florian Greten (Georg-Speyer-Haus, Frankfurt/M.) we found that these mutant mice show an increased tendency to develop inflammation-induced tumors", says Hermeking. Notably, these

miR-34a-deficient tumors invaded into neighbouring tissue, which was not observed in normal mice. Using cultured cells derived from human tumors of the breast and prostate gland, they confirmed that the IL6R/STAT3/miR-34a feedback loop is also activated in other tumor types. "Furthermore, analysis of tumor samples from large cohorts of colorectal cancer patients revealed that activation of the loop is associated with metastasis", Hermeking reports.
The new results show that miR-34a inactivation contributes to metastasis by activating the oncogenic IL-6R/STAT3 pathway. The discovery of this feedback mechanism also offers a number of targets for therapeutic intervention. In addition to STAT3 and IL-6, which are already targeted by a number of anti-tumor agents, the new study directs attention to the potential of miR-34a as a further focus of drug development for the treatment of metastasizing colon tumors. "We have previously shown that the miR-34a gene is often epigenetically inactivated by CpG methylation in tumors, which are more likely to metastasize. Detection of miR-34a inactivation may therefore represent a useful prognostic marker", says Hermeking.

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Titanium clubs can cause golf course fires, UCI study finds

Sparks fly when head hits rocks in the rough, potentially igniting brush

Irvine, Calif. - Titanium alloy golf clubs can cause dangerous wildfires, according to UC Irvine scientists. When a club coated with the lightweight metal is swung and strikes a rock, it creates sparks that can heat to more than 3,000 degrees Fahrenheit for long enough to ignite dry foliage, according to findings published recently in the peer-reviewed journal Fire and Materials.
Orange County, Calif., fire investigators asked UC Irvine to determine whether such clubs could have caused blazes at Shady Canyon Golf Course in Irvine and Arroyo Trabuco Golf Club in Mission Viejo a few years ago.
"One fire almost reached homes before they stopped it. This unintended hazard could potentially lead to someone's death," said chemical engineering & materials science professor James Earthman, lead author on the paper. "A very real danger exists, particularly in the Southwest, as long as certain golf clubs remain in use."
He suspected that the titanium heads on some clubs designed for use in "the rough" – natural areas off irrigated fairways – could be to blame for the fires. Most golf clubs have stainless steel heads. However, a significant number being manufactured or in circulation have a titanium alloy component in the head. Such alloys are 40 percent lighter, which can make the club easier to swing, including when chipping errant balls out of tough spots. In Southern California, those spots are often in flammable scrub brush.
The researchers painstakingly re-created in the lab course conditions on the days of the fires. Using high-speed video cameras and powerful scanning electron microscope analysis, they found that when titanium clubs were abraded by striking or grazing hard surfaces, intensely hot sparks flew out of them. In contrast, when standard stainless steel clubs were used, there was no reaction.
"Rocks are often embedded in the ground in these rough areas of dry foliage," Earthman noted. "When the club strikes a ball, nearby rocks can tear particles of titanium from the sole of the head. Bits of the particle surfaces will react violently with oxygen or nitrogen in the air, and a tremendous amount of heat is produced. The foliage ignites in flames."
Co-authors on the paper are Janahan Arulmoli, Bryant Vu, Ming-Je Sung and Farghalli Mohamed, also from UC Irvine.

http://nyti.ms/1rc4W2s

Protein May Hold the Key to Who Gets Alzheimer's

It is one of the big scientific mysteries of Alzheimer's disease: Why do some people whose brains accumulate the plaques and tangles so strongly associated with Alzheimer's not develop the disease?

By PAM BELLUCKMARCH 19, 2014

Now, a series of studies by Harvard scientists suggests a possible answer, one that could lead to new treatments if confirmed by other research. The memory and thinking problems of Alzheimer's disease and other dementias, which affect an estimated seven million Americans, may be related to a failure in the brain's stress response system, the new research suggests. If this system is working well, it can protect the brain from abnormal Alzheimer's proteins; if it gets derailed, critical areas of the brain start degenerating.
"This is an extremely important study," said Li-Huei Tsai, director of the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology, who was not involved in the research but wrote a commentary accompanying the study. "This is the first study that is really starting to provide a plausible pathway to explain why some people are more vulnerable to Alzheimer's than other people."
The research, published on Wednesday in the journal Nature, focuses on a protein previously thought to act mostly in the brains of developing fetuses. The scientists found that the protein also appears to protect neurons in healthy older people from aging-related stresses. But in people with Alzheimer's and other dementias, the protein is sharply depleted in key brain regions.

Experts said if other scientists could replicate and expand upon the findings, the role of the protein, called REST, could spur development of new drugs for dementia, which has so far been virtually impossible to treat. But they cautioned that much more needed to be determined, including whether the decline of REST was a cause, or an effect, of brain deterioration, and whether it was specific enough to neurological diseases that it could lead to effective therapies.

"You're going to see a lot of papers now following up on it," said Dr. Eric M. Reiman, executive director of the Banner Alzheimer's Institute in Phoenix, who was not involved in the study. "While it's a preliminary finding, it raises an avenue that hasn't been considered before. And if this provides a handle on which to understand normal brain aging, that will be great, too."

REST, a regulator that switches off certain genes, is primarily known to keep fetal neurons in an immature state until they develop to perform brain functions, said Dr. Bruce A. Yankner, a professor of genetics at Harvard Medical School and the lead author of the new study. By the time babies are born, REST becomes inactive, he said, except in some areas outside the brain like the colon, where it seems to suppress cancer.

While investigating how different genes in the brain change as people age, Dr. Yankner's team was startled to find that REST was the most active gene regulator in older brains.

"Why should a fetal gene be coming on in an aging brain?" he wondered. He hypothesized that it was because in aging, as in birth, brains encounter great stress, threatening neurons that cannot regenerate if harmed.

His team discovered that REST appears to switch off genes that promote cell death, protecting neurons from normal aging processes like energy decrease, inflammation and oxidative stress.

Analyzing brains from brain banks and dementia studies, the researchers found that brains of young adults ages 20 to 35 contained little REST, while healthy adults between the ages of 73 and 106 had plenty. REST levels grew the older people got, so long as they did not develop dementia, suggesting that REST is related to longevity.

But in people with Alzheimer's, mild cognitive impairment, frontotemporal dementia and Lewy body dementia, the brain areas affected by these diseases contained much less REST than healthy brains.

This was true only in people who actually had memory and thinking problems. People who remained cognitively healthy, but whose brains had the same accumulation of amyloid plaques and tau tangles as people with Alzheimer's, had three times more REST than those suffering Alzheimer's symptoms. About a third of people who have such plaques will not develop Alzheimer's symptoms, studies show.

REST levels dropped as symptoms worsened, so people with mild cognitive impairment had more REST than Alzheimer's patients. And only key brain regions were affected. In Alzheimer's, REST steeply declined in the prefrontal cortex and hippocampus, areas critical to learning, memory and planning. Other areas of the brain not involved in Alzheimer's showed no REST drop-off. It is not yet possible to analyze REST levels in the brains of living people, and several Alzheimer's experts said that fact limited what the new research could prove.

John Hardy, an Alzheimer's researcher at University College London, cautioned in an email that information from post-mortem brains could not prove that a decline in REST caused dementia because death might produce unrelated damage to brain cells.

To investigate further, the team conducted what both Dr. Tsai and Dr. Reiman called a "tour de force" of research, examining REST in mice, roundworms and cells in the lab.

"We wanted to make sure the story was right," Dr. Yankner said. "It was difficult to believe at first, to be honest with you." Especially persuasive was that mice genetically engineered to lack REST lost neurons as they aged in brain areas afflicted in Alzheimer's. Dr. Yankner said REST appeared to work by traveling to a neuron's nucleus when the brain was stressed. In dementia, though, REST somehow gets diverted, traveling with toxic dementia-related proteins to another part of the neuron where it is eventually destroyed.

Experts said the research, while intriguing, left many unanswered questions. Bradley Wise of the National Institute on Aging's neuroscience division, which helped finance the studies, said REST's role needed further clarification. "I don't think you can really say if it's a cause of Alzheimer's or a consequence of Alzheimer's" yet, he said.

Dr. Samuel E. Gandy, an Alzheimer's researcher at Mount Sinai Medical Center, wondered if REST figured only in neurodegenerative diseases or in other diseases, too, which could make it difficult to use REST to develop specific treatments or diagnostic tests for dementia. "My ambivalence is, is this really a way that advances our understanding of the disease or does this just tell us this is even more complicated than we thought?" he said.

Dr. Yankner's team is looking at REST in other neurological diseases, like Parkinson's. He also has thoughts about a potential treatment, lithium, which he said appears to stimulate REST function, and is considered relatively safe.

But he and other experts said it was too early. “I would hesitate to start rushing into lithium treatment” unless rigorous studies showed that it could forestall dementia, said Dr. John C. Morris, an Alzheimer’s researcher at Washington University in St. Louis.
Still, Dr. Morris said, the REST research the team conducted so far is “very well done, and certainly helps support this idea that we’ve all tried to understand about why Alzheimer’s is age-associated and why, while amyloid is necessary for the development of Alzheimer’s disease, it certainly is not sufficient.”
He added, “There have to be some other processes and triggers that result in Alzheimer’s.”
Correction: March 19, 2014
Because of an editing error, an earlier version of this article misstated the gender of Dr. Li-Huei Tsai. Dr. Tsai is a woman.

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Surgery after major stroke also improves survival odds in elderly patients

In patients over 60, hemicraniectomies save lives but do not prevent severe disability / Clinical study led by Heidelberg University Hospital's Neurology and Neurosurgery published in New England Journal of Medicine

Patients who are over the age of 60 and have suffered a major stroke due to blockage of the middle cerebral artery benefit from hemicraniectomy – removal of part of the skull located above the affected brain tissue. The procedure relieves increased pressure on the brain in the first 48 hours after the stroke. These patients' chances of survival increase two-fold if they undergo surgery. However, patients who have been operated on often survive with severe disabilities, while patients who do not undergo the surgery generally die quickly. These findings were obtained in a study conducted by 13 German stroke centers led by Heidelberg University Hospital's Departments of Neurology and Neurosurgery and have been published in the current issue of the renowned New England Journal of Medicine.
"For the first time, it has now been proven that for a cohort of elderly patients too, hemicraniectomy can save lives," explained Professor Werner Hacke, Medical Director of Heidelberg University Hospital's Department of Neurology. A study published 5 years ago showed that in patients below the age of 60, the results of the procedure are more favorable (see Lancet Neurology, 2007 under Literature). "In younger patients, the surgery tripled the chances of survival. In addition, they rarely sustained severe disabilities," said Professor Andreas Unterberg, Medical Director at Heidelberg University Hospital's Department of Neurosurgery. "We were not surprised by the lower treatment effect in the current study, since we know that the older a stroke patient, the poorer his or her prognosis."

Elderly patients: Overall poorer prognosis after severe stroke

The prognosis in patients with a blockage of the middle cerebral artery is very poor. In nearly 80% of the patients, without surgery, it causes death in a matter of days, even if they receive the maximum possible conservative intensive care. The necrotic brain tissue and its surroundings expand due to brain swelling (edema) and intracranial pressure severely increases, destroying vitally important brain tissue. The decompression surgery provides space for the swollen brain tissue in the critical phase. The exposed brain is covered with a protective membrane. Once brain swelling has decreased, the removed bone flap is replaced. The procedure has low risks, can be performed quickly and has few complications. Since its efficacy was proven in younger patients (below 60), it has become the standard treatment at many stroke centers. The surgery reduced mortality in younger patients from a rate of over 70% to around 20%.

Strict indications and additional studies warranted

The results of the current study are highly significant for the treatment of elderly stroke patients. The analysis includes 112 patients between the ages of 61 and 82 who had experienced a severe stroke and were treated with intensive care only or who underwent a hemicraniectomy within 48 hours of the stroke. The study was already stopped after the inclusion of 83 patients due to the clear superiority of the surgical procedure. The use of hemicraniectomies reduced the mortality rate from 70% to 33%. However, the proportion of very severely disabled patients in the group undergoing the procedure was nearly 30%.
"Many patients do not accept the notion of survival with severe disability, especially in very old age," Professor Unterberg reported. "For this reason, in older patients in particular, the pros and cons of the procedure must be discussed with the patients and their families," Professor Hacke added. Neurosurgeons and neurologists therefore need to discuss this type of treatment with patients and their families. Further studies may succeed in finding out which older patients especially will benefit from a hemicraniectomy.
Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke; Jüttler, E., Unterberg, A., Woitzik, J. , Bösel, J., Amiri, H., Sakowitz, O., Gondan, M., Schiller, P., Lamprecht, R., Luntz, S., Schneider, H., Pinzer, Th., Hobohm, C., Meixensberger, J., and Hacke W., for the DESTINY II Investigators , N Engl J Med. 2014 March 20;370(12):1-9. DOI: 10.1056/NEJMoa1311367

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http://www.eurekalert.org/pub_releases/2014-03/ps-3ml031714.php#rssowlmlink

3-D model links facial features and DNA

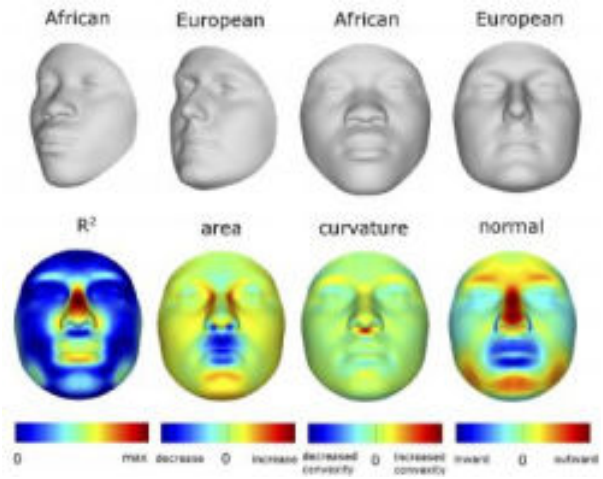
DNA can already tell us the sex and ancestry of unknown individuals, but now an international team of researchers is beginning to connect genetics with facial features, degrees of femininity and racial admixture.

"By jointly modeling sex, genomic ancestry and genotype, the independent effects of particular alleles on facial features can be uncovered," the researchers state today (Mar. 20) in PLOS Genetics. They add that "by simultaneously modeling facial shape variation as a function of sex and genomic ancestry along with genetic markers in craniofacial candidate genes, the effects of sex and ancestry can be removed from the model thereby providing the ability to extract the effects of individual genes."

In essence, by including sex and racial admixture, researchers can learn about how certain genes and their variations influence the shape of the face and its features. "We use DNA to match to an individual or identify an individual, but you can get so much more from DNA," said Mark D. Shriver, professor of anthropology, Penn State. "Currently we can't go from DNA to a face or from a face to DNA, but it should be possible."

The researchers looked at both actual physical face shape and genetic markers of face shape. They then validated their study by asking individuals to look at faces and determine four things. Is this face male or female? How feminine is it? What proportion of this person is West African? What group would you put this person in, Black African or African-American; White, European or European-American; or Mixed?

To look at the physical face shape, the researchers used populations of mixed West African and European ancestry from the U.S., Brazil and Cape Verde. They placed a grid on 3-D images of the faces of the subjects and measured the spatial coordinates of the grid points. They then used statistical methods to determine the relationship between the variation in the faces and the effects of sex, genomic ancestry and genes that affect the shape of the head and face.



Facial features are affected by the response-based imputed variable for ancestry. First row shows the range of facial features three standard deviations to either side of the mean in profile and full face. Second row shows (left to right) the proportion of the total variation, and three primary facial shape change parameters:area ratio, curvature difference and normal displacement. **Shriver/Claes**

To identify these genes, the researchers looked at known genetic mutations that cause facial and cranial deformation because these genes in their normal variations might also affect the face and head. For example, one gene affects the lips, another changes the shape and configuration of the bones around the eyes, and another influences the shape of the mid face and skull.

"Probably only 5 percent of genes show a difference between populations," said Shriver. "We are using different populations because they have had different environments and different social environments."

The researchers look at the face because it is the most visible part of humans, and characteristics are likely to be influenced by selection. The environment, the local temperatures, rainfall, elevation or other factors in the surroundings may influence certain physical features. Other facial characteristics may be influenced by sexual selection, a recognized or unrecognized preference for a certain look. This changes from group to group and may have no influence on survivability but are instead related to mate choice and contest competition. Both forms of selection will concentrate certain variations in geological areas over time. By looking at groups of mixed ancestry, the researchers can more easily identify the different variations.

"The environment and social environment are major driving factors in changing a whole set of genes that make up how a person looks," said Peter Claes, postdoctoral researcher, research expert in morphometrics, Medical Imaging Research Center, KU Leuven, Belgium and first author on the paper.

Eventually, the researchers think that they might approximate the image of a parent from the DNA of children or better visualize some of Homo sapiens' ancestors by looking at DNA. On a more practical level, law

enforcement groups might be able to create a "mug shot" from DNA to identify both victims and criminals. These predictive models fashioned from DNA would be forensically useful.

Other researchers at Penn State included David A. Puts, associate professor of anthropology; Denise K. Lieberton, recent Ph.D. recipient in anthropology; Kerri Matthes Rosana, recent M.S. graduate in genetics; Ellen E. Quillen, recent Ph.D. in anthropology; Laurel N. Pearson, recent Ph.D. in genetics and current postdoctoral fellow in anthropology; Marc Bauchet, Ph.D. graduate in anthropology; Arslan A. Zaidi and Wei Yao, graduate students in genetics.

Other institutions involved with this project include Smurfitt Institute of Genetics, Dublin; Stanford University; HudsonAlpha Institute for biotechnology, Huntsville, Alabama; Universidade do Porto, Portugal; Universidade Católica de Brasília; University of Western Australia, Perth; Murdoch University, Perth; King Edward Memorial Hospital, Perth; University of Pennsylvania, Philadelphia; and University of Connecticut, Storrs.

The National Science Foundation, the National Institute of Justice and the National Institutes of Health supported this research.

http://www.eurekalert.org/pub_releases/2014-03/ki-nam031814.php#rssowlmlink

New approach makes cancer cells explode

Researchers at Karolinska Institutet in Sweden have discovered that a substance called Vacquinol-1 makes cells from glioblastoma, the most aggressive type of brain tumour, literally explode.

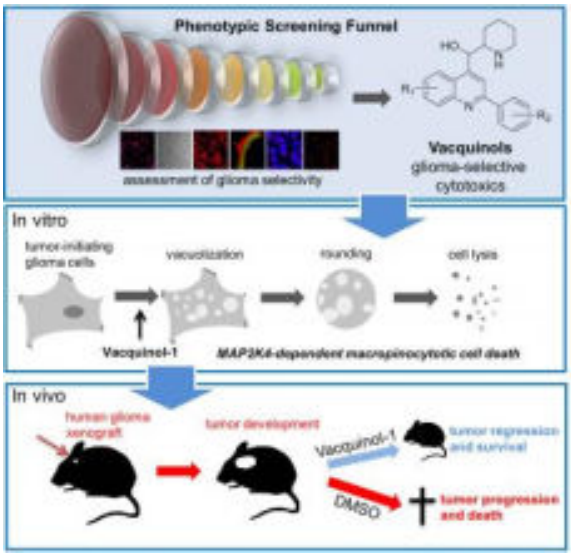
When mice were given the substance, which can be given in tablet form, tumour growth was reversed and survival was prolonged. The findings are published in the journal Cell.

The established treatments that are available for glioblastoma include surgery, radiation and chemotherapy. But even if this treatment is given the average survival is just 15 months. It is therefore critical to find better treatments for malignant brain tumours.

Researchers at Karolinska Institutet and colleagues at Uppsala University have discovered an entirely new mechanism to kill tumour cells in glioblastoma. Researchers in an initial stage have exposed tumour cells to a wide range of molecules. If the cancer cells died, the molecule was considered of interest for further studies, which initially applied to over 200 kinds of molecules. Following extensive studies, a single molecule has been identified as being of particular interest. The researchers wanted to find out why it caused cancer cell death.

It was found that the molecule gave the cancer cells an uncontrolled vacuolization, a process in which the cell carries substances from outside the cell into its interior. This carrying process is made via the vacuoles, which can roughly be described as blisters or bags consisting of cell membranes. The process is similar to what was behind last year's Nobel Prize in physiology or medicine, the discovery that describes how cellular vesicles move things from the interior of the cell to its surface. When cancer cells were filled with a large amount of vacuoles, the cell membranes (the outer wall of the cell) collapsed and the cell simply exploded and necrotized.

"This is an entirely new mechanism for cancer treatment. A possible medicine based on this principle would therefore attack the glioblastoma in an entirely new way. This principle may also work for other cancer diseases, we have not really explored this yet," says Patrik Ernfors, professor of tissue biology at the Department of Medical Biochemistry and Biophysics at Karolinska Institutet.



In a paper in the journal Cell, researchers at Karolinska Institutet show that Vacquinol-1 makes cells from glioblastoma literally explode. **Patrik Ernfors and colleagues**

Researchers made mice that had human glioblastoma cells transplanted ingest the substance for five days. The average survival was about 30 days for the control group that did not receive the substance. Of those who received the substance six of eight mice were still alive after 80 days. The study was then considered of such interest that the scientific journal wanted to publish the article immediately.

"We now want to try to take this discovery in basic research through preclinical development and all the way to the clinic. The goal is to get into a phase 1 trial," says Patrik Ernfors.

The study has been funded with money from the Swedish Research Council, the Swedish Cancer Society, the Swedish Foundation for Strategic Research, the Brain Foundation, Hållsten's Research Foundation, the Torsten Söderberg Foundation and Wallenberg Scholar.

Publication: 'Vulnerability of glioblastoma cells to catastrophic vacuolization and death induced by a small molecule', Satish Srinivas Kitambi, Enrique M Toledo, Dmitry Usoskin, Shimei Wee, Aditya Harisankar, Richard Svensson, Kristmundur Sigmundsson, Christina Kalderén, Mia Niklasson, Soumi Kundu, Sergi Aranda, Bengt Westermark, Lene Uhrbom, Michael Andäng, Peter Damberg, Sven Nelander, Ernest Arenas, Per Artursson, Julian Walfridsson, Karin Forsberg Nilsson, Lars G. J. Hammarström & Patrik Ernfors, Cell, online 20 March 2014, 10 April 2014 paper issue.

http://www.eurekalert.org/pub_releases/2014-03/ru-sss031814.php#rssowlmlink

Sniff study suggests humans can distinguish more than 1 trillion scents

The human sense of smell does not get the respect it deserves, new research suggests.

In an experiment led by Andreas Keller, of Rockefeller's Laboratory of Neurogenetics and Behavior, researchers tested volunteers' ability to distinguish between complex mixtures of scents. Based on the sensitivity of these people's noses and brains, the team calculated the human sense of smell can detect more than 1 trillion odor mixtures, far more discrete stimuli than previous smell studies have estimated.

The existing generally accepted number is just 10,000, says Leslie Vosshall, Robert Chemers Neustein Professor and head of the laboratory. "Everyone in the field had the general sense that this number was ludicrously small, but Andreas was the first to put the number to a real scientific test," Vosshall says.

In fact, even 1 trillion may be understating it, says Keller. "The message here is that we have more sensitivity in our sense of smell than for which we give ourselves credit. We just don't pay attention to it and don't use it in everyday life," he says.

The quality of an odor has multiple dimensions, because the odors we encounter in real life are composed of complex mixes of molecules. For instance, the characteristic scent of rose has 275 components, but only a small percentage of those dominate the perceived smell. That makes odor much more difficult to study than vision and hearing, which require us to detect variations in a single dimension. For comparison, researchers estimate the number of colors we can distinguish at between 2.3 and 7.5 million and audible tones at about 340,000.

To overcome this complexity, Keller combined odors and asked volunteers whether they could distinguish between mixtures with some components in common. "Our trick is we use mixtures of odor molecules, and we use the percentage of overlap between two mixtures to measure the sensitivity of a person's sense of smell," Keller says. To create his mixtures, Keller drew upon 128 odor molecules responsible for scents such as orange, anise and spearmint. He mixed these in combinations of 10, 20 and 30 with different proportions of components in common. The volunteers received three vials, two of which contained identical mixes, and they were asked to pick out the odd one.

This approach was inspired by previous work at the Weizmann Institute in Israel, in which researchers combined odors at similar intensities to create neutral smelling "olfactory white." In that experiment and in Keller's study, the researchers were interested in the perception of odor qualities, such as fishy, floral or musky – not their intensity. But since intensity can interfere with the perceived qualities, both had to account for it.

The results, published this week in Science, show that while individual volunteers' performance varied greatly, on average they could tell the difference between mixtures containing as much as 51 percent of the same components. Once the mixes shared more than half of their components, fewer volunteers could tell the difference between them. This was true for mixes of 10, 20 and 30 odors.

By analyzing the data, the researchers could calculate the total number of distinguishable mixtures.

"It turns out that the resolution of the olfactory system is not extraordinary – you need to change a fair fraction of the components before the change can be reliably detected by more than 50 percent of the subjects," says collaborator Marcelo O. Magnasco, head of the Laboratory of Mathematical Physics at Rockefeller. "However, because the number of combinations is quite literally astronomical, even after accounting for this limitation the total number of distinguishable odor combinations is quite large." The 1 trillion estimate is almost certainly too low, the researchers say, because there are many, many more odor molecules in the real world that can be mixed in many more ways.

Keller theorizes that our ancestors had much more use and appreciation for our sense of smell than we do. Humans' upright posture lifted our noses far from the ground where most smells originate, and more recently, conveniences such as refrigerators and daily showers, have effectively limited odors in the modern world. "This could explain our attitude that smell is unimportant, compared to hearing and vision," he says.

Nevertheless, the sense of smell remains closely linked to human behavior, and studying it can tell us a lot about how our brains process complex information. The results of this study are a step toward an elusive quantitative science of odor perception that can help drive further research, Keller says.

http://www.eurekalert.org/pub_releases/2014-03/uocd-tgf032014.php#rssowlmlink

The gene family linked to brain evolution is implicated in severity of autism symptoms

New study on DUF1220

The same gene family that may have helped the human brain become larger and more complex than in any other animal also is linked to the severity of autism, according to new research from the University of Colorado Anschutz Medical Campus. The gene family is made up of over 270 copies of a segment of DNA called DUF1220. DUF1220 codes for a protein domain – a specific functionally important segment within a protein.

The more copies of a specific DUF1220 subtype a person with autism has, the more severe the symptoms, according to a paper published in the PLoS Genetics.
This association of increasing copy number (dosage) of a gene-coding segment of DNA with increasing severity of autism is a first and suggests a focus for future research into the condition Autism Spectrum Disorder (ASD). ASD is a common behaviorally defined condition whose symptoms can vary widely – that is why the word "spectrum" is part of the name. One federal study showed that ASD affects one in 88 children.
"Previously, we linked increasing DUF1220 dosage with the evolutionary expansion of the human brain," says James Sikela, PhD, a professor in the Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine. Sikela is the corresponding author of the study that was just published.
"One of the most well-established characteristics of autism is an abnormally rapid brain growth that occurs over the first few years of life. That feature fits very well with our previous work linking more copies of DUF1220 with increasing brain size. This suggests that more copies of DUF1220 may be helpful in certain situations but harmful in others."
The research team found that not only was DUF1220 linked to severity of autism overall, they found that as DUF1220 copy number increased, the severity of each of three main symptoms of the disorder -- social deficits, communicative impairments and repetitive behaviors – became progressively worse.
In 2012, Sikela was the lead scientist of a multi-university team whose research established the link between DUF1220 and the rapid evolutionary expansion of the human brain. The work also implicated DUF1220 copy number in brain size both in normal populations as well as in microcephaly and macrocephaly (diseases involving brain size abnormalities).
The first author of the autism study, Jack Davis, PhD, who contributed to the project while a postdoctoral fellow in the Sikela lab, has a son with autism and thus had a very personal motivation to seek out the genetic factors that cause autism. The research by Davis, Sikela and colleagues at the Anschutz campus in Aurora, Colo., focused on the presence of DUF1220 in 170 people with autism.
Strikingly, Davis says, DUF1220 is as common in people who do not have ASD as in people who do. So the link with severity is only in people who have the disorder. "Something else is at work here, a contributing factor that is needed for ASD to manifest itself," Davis says. "We were only able to look at one of the six different subtypes of DUF1220 in this study, so we are eager to look at whether the other subtypes are playing a role in ASD."
Because of the high number of copies of DUF1220 in the human genome, the domain has been difficult to measure. As Sikela says, "To our knowledge DUF1220 copy number has not been directly examined in previous studies of the genetics of autism and other complex human diseases .So the linking of DUF1220 with ASD is also confirmation that there are key parts of the human genome that are still unexamined but are important to human disease."

http://www.eurekalert.org/pub_releases/2014-03/uosd-nem032114.php#rssowlmlink

Now even more likely that there are particles smaller than Higgs out there

Nobody has seen them yet; particles that are smaller than the Higgs particle.

However theories predict their existence, and now the most important of these theories have been critically tested. The result: The existence of the yet unseen particles is now more likely than ever.
"I gave them a very critical review", says Thomas Ryttov, particle physicist and associate professor at the Center for Cosmology and Particle Physics Phenomenology (CP ³ - Origins), University of Southern Denmark. He refers to the theories, that over the last app. five years have been put forward for the existence of particles in the universe that are smaller than the Higgs particle. Having given these theories a critical review, he finds no new signs of weakness in them:
"There seems to be no new or unseen weaknesses. My review just leaves them just stronger", he says.
Over the past 5-8 years, a handful of theories have drawn particular interest from particle physicists. They all predict that there must be one or more types of particles that are even smaller than the Higgs particle. So far it has however not been possible to prove their existence.
"Here at CP ³ - Origins, we are interested in the pursuit of such as yet unknown particles. We know that there must be a force that binds them together so that they together can create something bigger than themselves, something composite; a Higgs particle. It must happen similarly to quarks binding together to form protons and neutrons. If we can understand this force, we can explain and predict new physical phenomena like new particles", explains Thomas Ryttov.
This force is called the strong force. It cannot be compared to gravity, which also has the ability to keep two objects close together. The effect of gravity depends on the fact that the two objects are not too far from each

other, and the closer they are to each other the stronger the force of gravity will be. The strong force has the opposite effect: It is weak when two particles are close to each other, but strong - extremely strong - if you try to pull them apart.

Thomas Ryttov and his colleagues at CP ³ - Origins believe that the so-called techni-quarks can be the yet unseen particles, smaller than the Higgs particle. If techni-quarks exist they will form a natural exention of the Standard Model which includes three generations of quarks and leptons. These particles together with the fundamental forces form the basis of the observed matter in the universe.

Ref: Infrared fixed points in the minimal momentum subtraction scheme, Phys. Rev. D 89, 056001, 5 March 2014.

http://phys.org/news/2014-03-drill-core-evidence-credence-iron.html#rssowlmlink

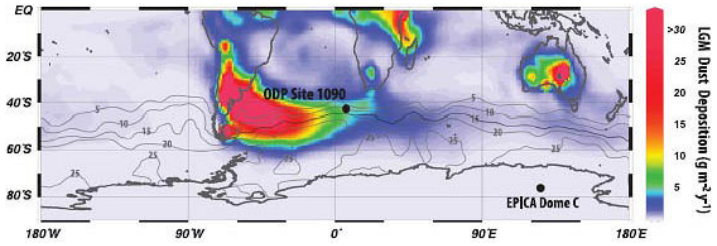
Drill core evidence adds credence to iron fertilization hypothesis regarding last ice age

Dust in the wind drove iron fertilization during ice age

Phys.org - An international team of researchers has found evidence in drill core samples taken near Antarctica that adds credence to the iron fertilization hypothesis. In their paper published in the journal Science, the team describes how lowered nitrogen levels found in core samples helps bolster the idea that increased iron in the oceans during the last ice age caused a decrease in atmospheric carbon dioxide levels.

Twenty years ago, oceanographer John Martin found evidence linking a decrease in atmospheric carbon dioxide levels during the last ice age, with an increase in ocean iron levels. It occurred, scientists reasoned, because iron is a vital nutrient for phytoplankton—when there is more iron, phytoplankton levels rise causing a fall in carbon dioxide levels because they pull it from the atmosphere. Until now however, there has been scant evidence to prove that the iron fertilization hypothesis is correct, though one group did try seeding a small part of the ocean and found localized phytoplankton levels increased along with a corresponding reduction in carbon dioxide levels. In this new effort, the researchers studied sea floor sediment core samples taken from the Sub-Antarctic Zone of the Southern Ocean.

In studying the core samples, the researchers analyzed the fossilized remains of tiny sea animals, specifically those with shells. Those shells hold evidence of what the creatures ate. The researchers found nitrogen levels that were lower than in similar creatures alive today. Lower nitrogen levels suggest a higher density of nitrate eating phytoplankton, which would have occurred due to higher levels of iron in the ocean. That iron, the researchers suggest made its way to the ocean via two separate avenues during the last ice age. The first was from the wind—dust from South America and Patagonia (due to different environmental conditions) blew across the ocean leaving iron deposits. The second was from river runoff.



Nitrogen is a critical building block for marine algae, yet the plankton in the Southern Ocean north of Antarctica leave much of it unused partly because they lack another needed nutrient, iron. The late John Martin hypothesized that dust-borne iron carried to the region by winds during ice ages may have fertilized the marine algae, allowing more of the Southern Ocean nitrogen to be used for growth and thus drawing CO2 into the ocean. To confirm Martin's hypothesis, the researchers measured isotopes of nitrogen in a sediment sample collected from a site that lies within the path of the winds that deposit iron-laden dust in the Subantarctic zone of the Southern Ocean (labeled ODP Site 1090). They found that the ratios of the types of nitrogen in the sample coincided with the predictions of Martin's hypothesis. The colors indicate simulated ice-age dust deposition from low to high (blue to red). The black contour lines show the concentrations of nitrate (a form of nitrogen) in modern surface waters. **Credit: Alfredo Martínez-García of ETH Zurich and Science/American Association for the Advancement of Science**

While the research results do add credence to the iron fertilization hypotheses, they likely also close the door on the possibly of dumping iron into the ocean to help reduce modern atmospheric carbon dioxide levels, as some scientists have suggested. The core samples indicate it would take approximately 1000 years of an increase in iron in the world's oceans to cause enough of an increase in phytoplankton to lower atmospheric carbon levels by just 40 parts per million.

More information: Iron Fertilization of the Subantarctic Ocean During the Last Ice Age, Science 21 March 2014: Vol. 343 no. 6177 pp. 1347-1350 DOI: 10.1126/science.1246848

ABSTRACT

John H. Martin, who discovered widespread iron limitation of ocean productivity, proposed that dust-borne iron fertilization of Southern Ocean phytoplankton caused the ice age reduction in atmospheric carbon dioxide (CO2). In a sediment core from the Subantarctic Atlantic, we measured foraminifera-bound nitrogen isotopes to reconstruct ice age nitrate consumption, burial fluxes of iron, and proxies for productivity. Peak glacial times and millennial cold events are characterized by increases in dust flux, productivity, and the degree of nitrate consumption; this combination is uniquely

consistent with Subantarctic iron fertilization. The associated strengthening of the Southern Ocean's biological pump can explain the lowering of CO2 at the transition from mid-climate states to full ice age conditions as well as the millennial-scale CO2 oscillations.

http://bit.ly/1fTdjqs

Rise of robot reporters: when software writes the news

Just three minutes after an earthquake hit California on Monday, the Los Angeles Times broke the story on its website.

17:00 21 March 2014 by Aviva Rutkin

The short article seemed fairly ordinary. It covered all the major details – when the quake hit, its magnitude and how far it spread. The only sign of anything unusual was the final sentence: "This post was created by an algorithm written by the author."

In other words, the article was put together by a robot.

Once readers realised that the story was computer-generated, it attracted a bit of attention. But quite a few machines already write the news. Forbes magazine uses a company named Narrative Science, based in Chicago, to report on corporate earnings. The same service partnered with ProPublica in January to create a news application concerned with equal access to education.

The earthquake algorithm, nicknamed QuakeBot, is not even the only robot reporter used by the Los Angeles Times. The newspaper's Mapping LA project uses bots to compare neighborhoods, and its website, The Homicide Report, automates posts about murders in the city.

While robot reporters are not yet able to file fascinating 2000-word features for New Scientist, early research suggests that they are not bad at all. A study published last month in Journalism Practice (doi:10/r2g) found that a small group of readers could not reliably discern whether a sports article was written by a human or a bot. Those assigned the automated article found it trustworthy and informative, albeit a bit boring.

"Would this replace real reporters? I would say no," says Christer Clerwall of Karlstads University in Karlsdad, Sweden, who led the study. He believes that robots will generally be stuck with the mundane types of stories that they already do, leaving more complex tasks like narrative and eyewitness reporting to the human journalists.

Robot reporters have plenty of benefits, says Quakebot creator Ken Schwenke.

"We had it up and we had it first and we had the information out for people," he says. "If we can automate it, why not?"

Just like famous statistician Nate Silver, who correctly predicted the last US election, robot journalists are all about data. They write stories by crunching spreadsheets full of sports scores, sales numbers, or stock market fluctuations. When it comes to pure computing power, bots will beat humans every time.

In QuakeBot's case, the process is a bit like the parlour game Mad Libs, in which players fill in gaps in ready-made sentences.

When the US Geological Survey sends an email alert about an earthquake of significant magnitude, the information zips over to Schwenke's web server. His bot parses through the email for the data, slots it into a prewritten template, and uploads the article to the newspaper's content management system. It even sends an email reminder for the editors to look it over.

Other approaches are a little more complex. Automated Insights, based in North Carolina, builds robot reporters that scour data for interesting trends. They focus on personalised stories that are only of interest to a small audience – like recaps of fantasy football games on Yahoo, or summaries of recent web statistics.

In 2013, the company churned out 300 million pieces of content. Most journalists, says CEO Robbie Allen, want to write one article that will be read by lots of people. Automated Insight's goal is to do the opposite.

"We'll create a million pieces of content that we hope a million people read just one of," he says.

And as the number of sensors in the world grows – from lifelogging to environmental trackers – so too will the number of niche stories that robot reporters could potentially write about.

Now that robots can handle the basics of reporting, could editing be the next frontier?

At a panel on automated storytelling at Columbia Journalism School's Tow Center for Digital Journalism last month, Narrative Science co-founder Larry Birnbaum speculated on a system that could exercise editorial judgment. The bot would decide which stories were worth writing, how the stories should be written, and which readers to show them to.

"I would love to give readers and editors and algorithmic story generators an interface like this that says, you know, 'I understand there's a trade-off between brevity and content, or between timeliness and analysis,'" says Birnbaum. "This is just a gleaming in our eye, really, but this is something I'd love to build."

http://www.bbc.com/news/health-26703519##rssowlmlink

Family doctor services 'under threat of extinction'

A funding crisis and increased demand for care means general practice as patients know it in the UK is "under severe threat of extinction", the head of the Royal College of GPs has warned.

The royal college's president, Dr Maureen Baker, said failing to properly fund GP surgeries could have an impact on the sustainability of the NHS. Some practices were already closing due to lack of staff, she said.

The Department of Health said it recognised the "vital" job GPs do. Health think tank the King's Fund agreed that GP services were under increasing pressure, but said talk of "extinction" was "a huge exaggeration".

'Toxic mix'

While general practice deals with 90% of patient contact, it only receives 8.39% of the overall NHS budget, the RCGP said.

Dr Baker urged governments in London, Cardiff, Edinburgh and Belfast to take action to address the "huge and historic imbalance in funding". "General practice as we know it is now under severe threat of extinction," said Dr Baker. "It is imploding faster than people realise and patients are already bearing the brunt of the problem."

She said: "For generations, GPs have been the bedrock of the NHS and provided excellent care for patients. "But we can no longer guarantee a future for general practice as our patients know it, rely on it - and love it. "GPs are doing all they can but we are being seriously crippled by a toxic mix of increasing workloads and ever-dwindling budgets, which is leaving patients waiting too long for an appointment and not receiving the time or attention they need and that GPs want to give them."

'Grave concerns'

Funding for GPs is vital to protect the future of the NHS as a whole, Dr Baker said. "Cutting funding to the bone is a false economy - by investing in general practice, we are shoring up the rest of the NHS from collapse," she added. "We are fiddling while Rome burns and the four governments of the UK must wake up to the critical state that general practice is now in." If there is not sufficient funding in the 2014/15 budget rounds, the RCGP has "grave concerns for the sustainability of the NHS", according to its president.

The royal college says that funding for general practice in England has fallen by £400m in real terms over the past three years. In October, it published a report saying that £8.5bn had been invested in 2012-13, compared with £8.3bn in 2009-10, which is the equivalent of £8.9bn in 2012-13 prices. And in November, it published figures with the National Association for Patient Participation showing GP funding across the UK at a nine-year low.

Analysis

Nick Triggle Health correspondent

Spending less on something is not necessarily bad if it is a sign a service is becoming more efficient.

The figures quoted by the Royal College of GPs include funding for areas such as pay, IT and drugs. Arguments could be made that squeezing all three is justifiable.

Pay rises across the rest of the NHS - and the whole economy for that matter - have been suppressed in recent years. So why shouldn't GPs also share the pain?

Meanwhile, there has been a drive to increase the use of cheaper generic drugs and get better value for money out of IT systems.

The big question is really whether patient care is being hit. The government argues not, but not everyone agrees. There are plenty of GPs and patient groups that claim getting appointments is becoming more difficult as services are stretched.

Between 2004-05 and 2011-12, the proportion of the NHS budget spent on general practice had fallen from 9.47% to 7.78% in Scotland and from 8.58% to 7.77% in Wales, it said. In Northern Ireland, the figure dropped from 8.22% in 2010-11 to 8.1% in 2011-12.

Dr Baker told BBC Radio 5 live that while budgets had dwindled over the past three years, demand for GP services was increasing - from 300 million consultations in 2008 to 340 million in 2012. She warned that "in some areas, we believe that some practices are already shutting down". She welcomed government moves to train more medical staff, but called for immediate action "to shore up the service in the next few years, until these new doctors, nurses and support staff come on stream".

Increase in trainees

Prof Chris Ham, chief executive of health think tank the King's Fund, said that factors such as the ageing population and the complex needs of patients were putting GP surgeries under pressure, and he agreed their share of the NHS budget had fallen in recent years. But he added: "I'm not denying the real pressures and the lack of funding, but it's a massive leap from saying that to saying GPs face extinction." He said some surgeries were finding ways to cope with the pressures, including by offering more services by telephone and email.

An RCGP survey found that 62% of 1,007 people questioned thought the number of consultations carried out by GPs each day, believed to be between 40 and 60 in most cases, risks the standard of patient care they provide. More than a quarter, 28%, said the last time they tried to book an appointment with their doctor they could not get one in the same week. Four in 10 were worried that the amount of time they have to wait to see

their GP could affect their health. The poll, carried out by ComRes, also showed that 60% of the public want funding moved to general practice from other parts of the health service.
Shadow health secretary Andy Burnham said it was "simply unacceptable" that some patients had to wait up to a week for a GP appointment. He said this was putting pressure on hospital accident and emergency departments.
A DoH spokesperson said: "We recognise the vital job that GPs do.
"This is why we have cut GPs' targets by more than a third to free up more time with patients, and are dramatically increasing trainees so that GP numbers continue to grow faster than the population."
NHS England said its funding for GP services had increased by a third in real terms since 2002-03. It said recent changes to the GP contract would free up doctors' time by removing "rigid performance targets".

http://www.eurekalert.org/pub_releases/2014-03/jai-heb032114.php#rssowlmlink

HPV eradicated by AHCC supplement, preclinical study suggests

Japanese mushroom extract active hexose correlated compound (AHCC) may have role in prevention HPV-related cancers

Beaverton, OR - Treating cervical cancer cells with AHCC led to the eradication of HPV, human papillomavirus, as well as a decrease in the rate of tumor growth in-vitro and in-vivo, in research presented at the Society of Gynecological Oncology 45th Annual Meeting on Women's Cancer in Tampa, Florida. The study was led by Dr. Judith A. Smith, Pharm.D., at the University of Texas Health Science Center (UTHealth) Medical School at Houston.
In the study cervical cancer cells were treated with AHCC and incubated for 72 hours with sampling every 24 hours. The study was then repeated in two orthotopic mouse models, one HPV positive and other HPV negative control. The HPV expression was eradicated with once daily AHCC dosing for 90 days with durable response after 30 day observation off treatment. Dr. Smith then repeated the study to confirm findings and added sampling for correlative testing of immune markers to determine the mechanism by which AHCC eradicates the HPV virus.
These data suggest AHCC can eliminate HPV infections and may have a role in the prevention of HPV-related cancers. A confirmatory pilot study in HPV+ women is underway at UTHealth Women's Center.
"The results of this study were very encouraging," said Dr. Smith, Associate Professor at the UTHealth Medical School. "This study, initiated in 2008, shows that by itself AHCC has the potential to treat the HPV infection," she said. Smith's previous study evaluated AHCC integration with common chemotherapy agents used for the treatment of ovarian cancer, to screen for potential drug interactions and improvement in activity.
AHCC works as an immunotherapy, which is a treatment that uses a body's own immune system to help fight disease. Human and in-vivo studies have shown that AHCC increases the number and/or activity of Natural Killer (NK) cells, dendritic cells, and cytokines, which enable the body to effectively respond to infections and block the proliferation of tumors. http://ahccresearch.com/index.html
HPV (human papilloma virus) is the most common sexually transmitted virus in the United States. Up to 70% of sexually active adults will acquire HPV at some point in their lives. Human papillomavirus DNA has been detected in 99.7% of cervical cancer biopsies, yielding the largest causative relationship of any cancer. (1) According to the CDC several other types of cancer are also HPV related, including: 95% of anal cancer; 60% of oropharyngeal cancer; 65% of vaginal cancer; 50% of vulvar cancer; and 35% of penile cancer.
"I was intrigued by research presented at the annual AHCC symposium in Sapporo (2) showing the immune modulating effect of AHCC on other rare infections, and was eager to study the possibilities in treating the HPV infection associated with cervical cancer," said Dr. Smith.
"AHCC is a common, well tolerated nutritional supplement that has been used for decades in Japan, I am very excited to be pursuing a nutritional approach to trying to find a treatment for HPV infections," said Dr. Smith, whose research is on drug development for gynecologic cancers and conditions with a specific focus on drug interactions/drug resistance and integration of herbal and nutritional supplements for treatment of cancer.
"We had previously demonstrated an antiretroviral regimen that successfully eradicated the HPV infection but wanted to develop a more benign protocol, since these medications have a number of side effects," Dr. Smith continued.

1. Clinical Perspectives on the Role of the Human Papillomavirus Vaccine in the Prevention of Cancer, Justin M. Julius, Pharm.D., Lois Ramondeta, M.D., Katherine A. Tipton, Pharm.D., Lincy S. Lal, Pharm.D., Ph.D., Karen Schneider, M.D., Judith A. Smith, Pharm.D., FCCP, FISOPP Pharmacotherapy. 2011;31(3):280-297 http://onlinelibrary.wiley.com/doi/10.1592/phco.31.3.280/abstract;jsessionid=28484FCF040C2FE4843FABE7C391950A.f03t01

2. International Congress on Nutrition and Integrative Medicine (ICNIM) http://ahccresearch.com/annual-symposia.html

http://www.eurekalert.org/pub_releases/2014-03/vu-sei032114.php#rssowlmlink

Shifting evolution into reverse promises cheaper, greener way to make new drugs

This alternative approach to creating artificial organic molecules, called bioretrosynthesis, was first proposed four years ago by Brian Bachmann, associate professor of chemistry at Vanderbilt University.

Now Bachmann and a team of collaborators report that they have succeeded in using the method to produce the HIV drug didanosine. The proof of concept experiment is described in a paper published online March 23 by the journal Nature Chemical Biology.

"These days synthetic chemists can make almost any molecule imaginable in an academic laboratory setting," said Bachmann. "But they can't always make them cheaply or in large quantities. Using bioretrosynthesis, it is theoretically possible to make almost any organic molecule out of simple sugars."

Putting natural selection to use in this novel fashion has another potential advantage. "We really need a green alternative to the traditional approach to making chemicals. Bioretrosynthesis offers a method to develop environmentally friendly manufacturing processes because it relies on enzymes – the biological catalysts that make life possible – instead of the high temperatures and pressures, toxic metals, strong acids and bases frequently required by synthetic chemistry," he said.

Normally, both evolution and synthetic chemistry proceed from the simple to the complex. Small molecules are combined and modified to make larger and more complex molecules that perform specific functions. Bioretrosynthesis works in the opposite direction. It starts with the final, desired product and then uses natural selection to produce a series of specialized enzymes that can make the final product out of a chain of chemical reactions that begin with simple, commonly available compounds.

Bachmann got the idea of applying natural selection in reverse from the retro-evolution hypothesis proposed in 1945 by the late Caltech geneticist Norman Horowitz. Horowitz envisioned an early stage in the development of life where early organisms were swimming in a primordial soup rich in organic material. In this environment, imagine that one of the species finds a use for the complex chemical compound A that gives it a competitive advantage. As a result, its population expands, consuming more and more compound A. Everything goes well until compound A becomes scarce. When that happens, individuals who develop an enzyme that allows them to substitute the still plentiful compound B for the scarce compound A gain a reproductive advantage and continue to grow while those who remain dependent on compound A die out. And so it goes until many generations later the survivors have developed multi-step chemical pathways to produce the molecules that they need to survive from the molecules available in their environment.

To test Bachmann's retro approach, the Vanderbilt chemists first identified the drug that they wanted to produce – in this case didanosine, an anti-HIV drug sold under the trade names of Videx and Videx EC that is very costly to manufacture. Then they identified a similar "precursor" molecule that can be converted into didanosine when it is subject to a specific chemical transformation along with an enzyme capable of producing the type of transformation required. Once they identified the enzyme, the researchers made use of the power of natural selection by making thousands of copies of the gene that makes the enzyme using a special copying technique that introduces random mutations.

The mutant genes were transferred into the gut bacteria E. coli in order to produce the mutant enzymes and placed into different "wells." After the cells were broken open and the contents mixed with the precursor compound, the amount of didanosine, in each well was measured. The researchers selected the enzyme that produced the greatest amount of the desired drug and then made enough of this optimized enzyme for the next step.

Next the researchers identified a second precursor – an even simpler molecule that could be chemical converted into the first precursor – and an associated transformative enzyme. Again they made thousands of mutated versions of the transformative enzyme's gene, inserted them in E. coli, put them in wells, broke open the cells and mixed the content with the optimized enzyme and second precursor. Once again, they tested all the wells for the anti-HIV drug. The well with the highest level of didanosine was the one in which the mutant enzyme was most effective in making the first precursor, which the optimized enzyme then converted into didanosine. This gave them a second optimized enzyme. The researchers carried out this reverse selection process three times, until they could make didanosine out a simple and inexpensive sugar named dideoxyribose.

One of the key technical challenges was rapidly determining the three-dimensional structures of the enzymes that were generated during the evolutionary process. Associate Professor of Pharmacology Tina Iverson provided this capability. Her team analyzed the laboratory-evolved enzymes after each round of mutagenesis and identified how the structural changes caused by the mutations improved the enzyme's ability to produce the desired transformation.

This information helped the collaborators figure out why some mutant enzymes did a better job at producing the desired compounds than others, which guided their choices about the areas of the precursor proteins to target. The proof-of-concept experiment was performed in vitro instead of in living cells to keep things simple. However, the ultimate goal is to use the approach to produce artificial compounds by fermentation.
Graduate students William Birmingham, Chrystal Starbird, Timothy Panosian and David Nannemann contributed to the study. The research was supported by National Science Foundation graduate fellowship DGE 0909667, the D. Stanley and Ann T. Tarbell Endowment fund, National Institutes of Health grant GM079419 and Department of Energy Argonne National Laboratory contract DE-AC02-06CH11357

http://phys.org/news/2014-03-stars-newton-gravity-unchanged-cosmic.html#rssowlmlink

Exploding stars prove Newton's gravity unchanged over cosmic time

Australian astronomers have combined all observations of supernovae ever made to determine that the strength of gravity has remained unchanged over the last nine billion years.

Phys.org - Newton's gravitational constant, known as G, describes the attractive force between two objects, together with the separation between them and their masses. It has been previously suggested that G could have been slowly changing over the 13.8 billion years since the Big Bang. If G has been decreasing over time, for example, this would mean that the Earth's distance to the Sun was slightly larger in the past, meaning that we wouldexperience longer seasons now compared to at much earlier points in the Earth's history.

But researchers at Swinburne University of Technology in Melbourne have now analysed the light given off by 580 supernova explosions in the nearby and far Universe and have shown that the strength of gravity has not changed. "Looking back in cosmic time to find out how the laws of physics may have changed is not new" said Professor Jeremy Mould. "But supernova cosmology now allows us to do this with gravity."

A Type Ia supernova marks the violent death of a star called a white dwarf, which is as massive as our Sun but packed into a ball the size of our Earth. Our telescopes can detect the light from this explosion and use its brightness as a 'standard candle' to measure distances in the Universe, a tool that helped Australian astronomer Professor Brian Schmidt in his 2011 Nobel Prize winning work, discovering the mysterious force Dark Energy.

Professor Mould and his PhD student Syed Uddin at the Swinburne Centre for Astrophysics and Supercomputing and the ARC Centre of Excellence for All-sky Astrophysics (CAASTRO) assumed that these supernova explosions happen when a white dwarf reaches a critical mass or after colliding with other stars to 'tip it over the edge'.

"This critical mass depends on Newton's gravitational constant G and allows us to monitor it over billions of years of cosmic time – instead of only decades, as was the case in previous studies." said Professor Mould.

Despite these vastly different time spans, their results agree with findings from the Lunar Laser Ranging Experiment that has been measuring the distance between the Earth and the Moon since NASA's Apollo missions in the 1960s and has been able to monitor possible variations in G at very high precision.

"Our cosmological analysis complements experimental efforts to describe and constrain the laws of physics in a new way and over cosmic time." Mr Uddin said.

In their current publication, the Swinburne researchers were able to set an upper limit on the change in Newton's gravitational constant of 0.00000001% per year over the past nine billion years.

The ARC Centre of Excellence for All-sky Astrophysics (CAASTRO) is a collaboration between The Australian National University, The University of Sydney, The University of Melbourne, Swinburne University of Technology, the University of Queensland, The University of Western Australia and Curtin University, the latter two participating together as the International Centre for Radio Astronomy Research. CAASTRO is funded under the Australian Research Council Centre of Excellence program, with additional funding from the seven participating universities and from the NSW State Government's Science Leveraging Fund.

This research is published this month in the Publications of the Astronomical Society of Australia.

More information: Mould & Uddin "Constraining a possible variation of G with Type Ia supernovae" in PASA 2014. arxiv.org/abs/1402.1534

http://www.eurekalert.org/pub_releases/2014-03/w-uom032114.php#rssowlmlink

Use of mood-stabilizing drug linked with reduced risk of developing head and neck cancer

A new study indicates that a commonly used mood stabilizing drug may help prevent head and neck cancer.

The study is published early online in Cancer, a peer-reviewed journal of the American Cancer Society. Valproic acid (VPA) is currently prescribed as an anti-seizure medication and mood stabilizer, but it is also being studied as an anticancer agent because it inhibits histone acetyl transferases, which help control gene expression by changing DNA structure.

Johann Christoph Brandes MD, PhD, of the Atlanta Veterans Affairs Medical Center and Emory University in Atlanta, led a team that assessed the anticancer effects of VPA in a study of 439,628 veterans, of whom 26,911 were taking the medication for bipolar disorder, post-traumatic stress disorder, migraines, and seizures. Veterans who took VPA for at least one year had a 34 percent lower risk of developing head and neck cancer compared with those who did not take the medication. Higher doses and longer duration of VPA use seemed to provide additional benefits. No significant differences were observed for lung, bladder, colon, and prostate cancer incidences.

"A 34 percent risk reduction for the development of head and neck cancer with VPA use could result in the prevention of up to approximately 16,000 new cases and 3,000 to 4,000 annual deaths in the US alone," said Dr. Brandes. "Head and neck cancer is an important global health crisis, and low cost and low toxicity prevention strategies like VPA use have a high potential impact on pain, suffering, costs, and mortality associated with this disease."