http://bit.ly/1kaTcuL

Engineering earth-abundant catalysts that mimic platinum in renewable energy technologies

How to replace platinum-group metals with metals that are more plentiful

When one considers nonrenewable resources, the first to come to mind are fossil fuels: petroleum, coal, and natural gas. The rapid depletion of these unsustainable resources has sparked global research on renewable-energy technologies, such as fuel cells, electrolyzers, and lithium-air batteries.

Unfortunately there is a common unsustainable thread that links these burgeoning technologies: a dependence on platinum-group metals (PGMs). These elements - platinum, palladium, rhodium, iridium, ruthenium, and osmium - are the six least-abundant in the Earth's lithosphere, yet are the most stable and active catalysts. Even with efficient recycling, numerous studies have indicated that the Earth simply does not contain enough PGMs to support a global renewable-energy economy. Thus, PGMs can be considered unsustainable resources that are currently needed to enable renewable energy technologies.

MIT graduate student Sean Hunt, postdoc Tarit Nimmandwudipong, and Yuriy Román, an assistant professor of chemical engineering, have an idea for how to replace PGMs with metals that are more plentiful. In a paper published recently in the journal Angewandte Chemie, the team explained its process of synthesizing these alternative catalysts.

"Because the PGMs tend to be the most active and stable catalysts in virtually all relevant thermal and electrocatalytic processes, our research sought to answer an exciting question," Hunt explains. "Rather than finding new materials to replace PGMs in specific reactions, is it possible to modify the electron density of earth-abundant early transition metals [groups IV to VI on the periodic table] to catalytically mimic the PGMs?"

In the simplest sense, one can imagine that tungsten, with six valence electrons, can be electronically modified to mimic platinum, which has 10 valence electrons, by reacting it with carbon (four valence electrons) to give the ceramic material tungsten carbide (WC). Numerous studies have shown that WC is indeed platinumlike, and able to catalyze important thermo- and electrocatalytic reactions that tungsten metal cannot - such as biomass conversion, hydrogen evolution, oxygen reduction, and alcohol electrooxidation. Importantly, tungsten is more than three orders of magnitude more abundant than platinum in the Earth's crust, making it a viable material for a global renewable-energy economy.

However, both WC and platinum are heterogeneous catalysts, meaning that they require nanoparticle formulations to create high surface areas and invoke quantum confinement effects to maximize the rates of chemical reactions. While platinum nanoparticles are relatively easy to synthesize, until now, there have been no known methods to synthesize WC nanoparticles less than 5 nanometers and devoid of surface impurities. As Hunt explains, "Tungsten carbide forms at very high temperatures, typically over 800 degrees Celsius [1500 degrees Fahrenheit]. These high temperatures cause nanoparticles to sinter into large microparticles with low surface areas. Methods to date that alleviate this agglomeration instead result in nanoparticles that are covered with excess surface carbon. These surface impurities greatly reduce, or completely eliminate, the catalytic activity of WC."

To solve this problem, the MIT team developed a "removable ceramic coating method" by coating colloidally dispersed transition-metal oxide nanoparticles with microporous silica shells. At high temperatures, they show that reactant gases, such as hydrogen and methane, are able to diffuse through these silica shells and intercalate into the encapsulated metal oxide nanoparticles. This transforms the oxide nanoparticles into transition metal carbide (TMC) nanoparticles, while the silica shells prevent both sintering and excess carbon deposition. The silica shells can then be easily removed at room temperature, allowing the dispersal of nonsintered, metal-terminated TMC nanoparticles onto any high-surface-area catalyst support. This is the first method capable of this result.

The team has also been successful in synthesizing the first nonsintered, metal-terminated bimetallic TMC nanoparticles. Electrocatalytic studies have shown that these materials are able to perform hydrogen evolution and methanol electrooxidation at rates similar to commercial PGM-based catalysts, while maintaining activity over thousands of cycles. The catalytic activities obtained were more than two orders of magnitude better than commercial WC powders and WC nanoparticles made by current state-of-the-art synthesis methods that do not prevent sintering or surface carbon deposition. Next steps include the synthesis of other bimetallic TMCs, as well as transition metal nitride (TMN) nanoparticles. The team is investigating these materials for other electrocatalytic reactions as well as thermal catalytic reactions, such as hydrodeoxygenation for biomass reforming.

"This new method unlocks a broad range of monometallic and heterometallic transition metal carbide and nitride nanoparticles that researchers previously have been unable to synthesize or study," Román says. "While our research focuses mainly on the sustainable replacement of PGMs in thermal and electrocatalytic applications, we also anticipate broader impacts of our new TMC and TMN technologies outside catalysis. Because of their unique chemical, mechanical, and electronic properties, carbides and nitrides have garnered much attention for use in applications as diverse as supercapacitors, medical implants, optoelectronics, coatings, and high-temperature materials for the aerospace and nuclear sectors."

http://phys.org/news/2014-05-earth-survive-martian-conditions.html

Earth organisms survive under Martian conditions

New research suggests that methanogens - among the simplest and oldest organisms on Earth - could survive on Mars.

Phys.org - Methanogens, microorganisms in the domain Archaea, use hydrogen as their energy source and carbon dioxide as their carbon source, to metabolize and produce methane, also known as natural gas. Methanogens live in swamps and marshes, but can also be found in the gut of cattle, termites and other herbivores as well as in dead and decaying matter.

Methanogens are anaerobic, so they don't require oxygen. They don't require organic nutrients and are non-photosynthetic, indicating they could exist in sub-surface environments and therefore are ideal candidates for life on Mars.

Rebecca Mickol, a doctoral student in space and planetary sciences at the University of Arkansas, subjected two species of methanogens to Martian conditions: Methanothermobacter wolfeii and Methanobacterium formicicum. Both species survived the Martian freeze-thaw cycles that Mickol replicated in her experiments.

The species were tested for their ability to withstand Martian freeze-thaw cycles that are below the organisms' ideal growth temperatures: 37 degrees Celsius (98.6 degrees Fahrenheit) for M. formicicum and 55 degrees Celsius (131 degrees Fahrenheit) for M. wolfeii.

"The surface temperature on Mars varies widely, often ranging between minus 90 degrees Celsius and 27 degrees Celsius over one Martian day," Mickol said. "If any life were to exist on Mars right now, it would at least have to survive that temperature range. The survival of these two methanogen species exposed to long-term freeze/thaw cycles suggests methanogens could potentially inhabit the subsurface of Mars."

Mickol conducted the study with Timothy Kral, professor of biological sciences in the Arkansas Center for Space and Planetary Sciences and lead scientist on the project. She is presenting her work at the 2014 General Meeting of the American Society for Microbiology, being held May 17-20 in Boston.

The two species were selected because one is a hyperthermophile, meaning it thrives under extremely hot temperatures, and the other is a thermophile, which thrives under warm temperatures.

"The low temperature on Mars inhibited their growth, but they survived," Mickol said. "Once they got back to a warm temperature, they were able to grow and metabolize again. I wanted to see if these cold temperatures would kill them, or if they were able to survive and adapt."

Since the 1990s, Kral has been studying methanogens and examining their ability to survive on Mars. In 2004, scientists discovered methane in the Martian atmosphere, and immediately the question of the source became an important one. "When they made that discovery, we were really excited because you ask the question 'What's the source of that methane?'" Kral said. "One possibility would be methanogens."

http://www.eurekalert.org/pub_releases/2014-05/ssoa-tn051114.php

The next 'Big One' for the Bay Area may be a cluster of major quakes

Paleoseismic studies expand earthquake record back to 1600s

SAN FRANCISCO – A cluster of closely timed earthquakes over 100 years in the 17th and 18th centuries released as much accumulated stress on San Francisco Bay Area's major faults as the Great 1906 San Francisco earthquake, suggesting two possible scenarios for the next "Big One" for the region, according to new research published by the Bulletin of the Seismological Society of America (BSSA).

"The plates are moving," said David Schwartz, a geologist with the U.S. Geological Survey and co-author of the study. "The stress is re-accumulating, and all of these faults have to catch up. How are they going to catch up?"

The San Francisco Bay Region (SFBR) is considered within the boundary between the Pacific and North American plates. Energy released during its earthquake cycle occurs along the region's principal faults: the San Andreas, San Gregorio, Calaveras, Hayward-Rodgers Creek, Greenville, and Concord-Green Valley faults.

"The 1906 quake happened when there were fewer people, and the area was much less developed," said Schwartz. "The earthquake had the beneficial effect of releasing the plate boundary stress and relaxing the crust, ushering in a period of low level earthquake activity."

The earthquake cycle reflects the accumulation of stress, its release as slip on a fault or a set of faults, and its re-accumulation and re-release. The San Francisco Bay Area has not experienced a full earthquake cycle since its been occupied by people who have reported earthquake activity, either through written records or instrumentation. Founded in 1776, the Mission Dolores and the Presidio in San Francisco kept records of felt earthquakes and earthquake damage, marking the starting point for the historic earthquake record for the region.

"We are looking back at the past to get a more reasonable view of what's going to happen decades down the road," said Schwartz. "The only way to get a long history is to do these paleoseismic studies, which can help construct the rupture histories of the faults and the region. We are trying to see what went on and understand the uncertainties for the Bay Area."

Schwartz and colleagues excavated trenches across faults, observing past surface ruptures from the most recent earthquakes on the major faults in the area.

Radiocarbon dating of detrital charcoal and the presence of non-native pollen established the dates of paleoearthquakes, expanding the span of information of large events back to 1600.

The trenching studies suggest that between 1690 and the founding of the Mission Dolores and Presidio in 1776, a cluster of earthquakes ranging from magnitude 6.6 to 7.8 occurred on the Hayward fault (north and south segments), San Andreas fault (North Coast and San Juan Bautista segments), northern Calaveras fault, Rodgers Creek fault, and San Gregorio fault. There are no paleoearthquake data for the Greenville fault or northern extension of the Concord-Green Valley fault during this time interval. "What the cluster of earthquakes did in our calculations was to release an amount of energy somewhat comparable to the amount released in the crust by the 1906 quake," said Schwartz.

As stress on the region accumulates, the authors see at least two modes of energy release – one is a great earthquake and other is a cluster of large earthquakes. The probability for how the system will rupture is spread out over all faults in the region, making a cluster of large earthquakes more likely than a single great earthquake.

"Everybody is still thinking about a repeat of the 1906 quake," said Schwartz. "It's one thing to have a 1906-like earthquake where seismic activity is shut off, and we slide through the next 110 years in relative quiet. But what happens if every five years we get a magnitude 6.8 or 7.2? That's not outside the realm of possibility."

The paper, "The Earthquake Cycle in the San Francisco Bay Region: AD 1600-2012," will be published online May 20, 2014 by BSSA and will appear in the June print issue. BSSA is published by the Seismological Society of America, which is an international scientific society devoted to the advancement of seismology and the understanding of earthquakes for the benefit of society.

"The Earthquake Cycle in the San Francisco Bay Region: AD 1600-2012," published by BSSA. Authors: David Schwartz, USGS; James J. Lienkaemper, USGS; Suzanne Hecker, USGS; Keith I. Kelson, URS Corporation; Thomas E. Fumal, USGS; John N. Baldwin, Lettis Consultants International, Inc.; Gordon G. Seitz, California Geological Survey; Tina M. Niemi, University of Missouri-Kansas.

http://www.eurekalert.org/pub_releases/2014-05/uow-fnh051914.php

Favoritism, not hostility, causes most discrimination, says UW psychology professor

Most discrimination in the U.S. is not caused by intention to harm people different from us, but by ordinary favoritism directed at helping people similar to us, according to a theoretical review published online in American Psychologist.

"We can produce discrimination without having any intent to discriminate or any dislike for those who end up being disadvantaged by our behavior," said University of Washington psychologist Tony Greenwald, who co-authored the review with Thomas Pettigrew of the University of California, Santa Cruz.

Greenwald and Pettigrew reviewed experiments and survey methods from published scientific research on discrimination from the last five decades. They were surprised to find that the discrimination observed in those studies occurred much more often as helping rather than harming someone. But they also found that most researchers defined discrimination as based on negative attitudes and hostility, only rarely treating favoritism as a component of discrimination.

That makes sense, Greenwald said, because most people think of discrimination as the result of hostility: a white person spouting anti-black rhetoric, or a homophobe yelling slurs at a gay couple. But, he argues, it's more subtle acts, ones people don't even recognize as causing disadvantage to anyone, that are likely to be much more significant.

Take this hypothetical scenario: When conducting reviews of two employees, a manager finds they both fall between two performance categories. The manager gives a higher category to the employee whose child is friends with the manager's child, leading to a promotion and salary raise, while the other employee receives a smaller raise and no promotion.

Was the manager consciously discriminating against the second employee? Or did she simply give a boost to someone to whom she had an "ingroup" connection?

"Your 'ingroup' involves people that you feel comfortable with, people you identify with," Greenwald explained. "We usually think first of demographic characteristics like age, race, sex, religion and ethnicity as establishing an ingroup, but there are also ingroups based on occupation, neighborhood and schools attended, among other things. Outgroups are those with whom you don't identify."

Greenwald and Pettigrew propose that unequal treatment in the form of doing favors for those like you, rather than inflicting harm on those unlike you, causes the majority of discrimination in the U.S. "This is not to say that prejudice and hostility are not related to outgroup discrimination," Pettigrew said. "But they are not as central to most discrimination as ingroup favoritism."

Yet, historically, social scientists have emphasized prejudicial hostility as the root of discrimination.

"We looked at how prejudice has been defined in the history of psychology. It has generally been understood as hostility toward outgroups. That's easy to do, because inter-group conflict is an obvious fact of life," Greenwald said. "There are international conflicts, wars, gang battles, labor-management conflicts. When such conflicts are going on it's natural to think of them as rooted in hostility."

Greenwald hopes researchers will change how they study discrimination, because research results have substantial implications both for how discrimination is

identified and how it can be ameliorated in employment, health care, education and daily life.

He said overt acts of discrimination began to decline starting in the 1960s following civil rights laws. But prejudicial attitudes didn't necessarily change. What changed is that people were no longer legally allowed to act on their prejudices by, for example, denying housing to blacks or jobs to women.

The co-authors say that racial ingroup favoritism can be very subtle. For instance, if you work in an office that is mostly white and you're asked to recommend someone for a job opening, you're more likely to recommend someone who is like you and the rest of your ingroup.

This sort of ingroup favoritism happens at all ages and in different situations. Greenwald said it can happen on the playground, where children may exhibit ingroup favoritism based on race, economic class, or the same school or sports team.

"Hostility isn't integral to the definition of discrimination; you can treat people differently without being hostile to anyone," Greenwald said. "But it is societally important to understand how discrimination can occur both without hostility and without any intent to discriminate."

http://www.bbc.com/news/health-27466853

Prostate cancer 'may be a sexually transmitted disease'

Prostate cancer may be a sexually transmitted disease caused by a common yet often silent infection passed on during intercourse, scientists say - but experts say proof is still lacking.

By Michelle Roberts Health editor, BBC News online

Although several cancers are caused by infections, Cancer Research UK says it is too early to add prostate cancer to this list. The University of California scientists tested human prostate cells in the lab. They found a sex infection called trichomoniasis aided cancer growth. More research is now needed to confirm the link, they say in the journal Proceedings of the National Academy of Sciences (PNAS).

Sex infection

Trichomoniasis is believed to infect some 275 million people worldwide and is the most common non-viral sexually transmitted infection. Often, a person will have no symptoms and be unaware that they have it. Men may feel itching or irritation inside the penis, burning after urination or ejaculation, or a white discharge from the penis.

Women may notice itching or soreness of the genitals, discomfort with urination, or a discharge with an unpleasant fishy smell.

This latest research is not the first to suggest a link between trichomoniasis and prostate cancer. A study in 2009 found a quarter of men with prostate cancer showed signs of trichomoniasis, and these men were more likely to have advanced tumours. The PNAS study suggests how the sexually transmitted infection might make men more vulnerable to prostate cancer, although it is not definitive proof of such a link.

Prof Patricia Johnson and colleagues found the parasite that causes trichomoniasis - Trichomonas vaginalis - secretes a protein that causes inflammation and increased growth and invasion of benign and cancerous prostate cells.

They say more studies should now follow to further explore this finding - particularly since we still do not know what causes prostate cancer.

Nicola Smith, health information officer at Cancer Research UK, said: "This study suggests a possible way the parasite Trichomonas vaginalis could encourage prostate cancer cells to grow and develop more quickly.

"But the research was only done in the lab, and previous evidence in patients failed to show a clear link between prostate cancer and this common sexually transmitted infection. "There's been a lot of research into prostate cancer risk and we're working hard to piece together the puzzle.

"But there are still no known lifestyle factors that seem to affect the risk of developing the disease - and no convincing evidence for a link with infection. "The risk of prostate cancer is known to increase with age."

Prostate cancer is now the most common cancer in men in the UK - about one in nine men will get it at some point in their lives. It is more common in men over 70, and there appears to be some genetic risk since the disease can run in families.

http://www.wired.com/2014/05/hangover-cure/

Everything Science Knows About Hangovers - And How to Cure Them

Good morning, sunshine! You are so screwed.

By Adam Rogers

The light coming in through the window is so … there. You'd kill for a glass of water but die if it came with food. Your guts are in full rebellion; whatever happens next is going to happen in the bathroom. You have at least a couple of the following symptoms: headache, malaise, diarrhea, loss of appetite, fatigue, nausea, the shakes. You might also be dehydrated and feel generally slow - a little stupider, a little less coordinated.

You, my friend, have a hangover. And you can take heart in the fact that you're not alone. Some 77 percent of all drinkers report suffering from them. (The scientific term for the other 23 percent is "jerks.") But here's the amazing part: The underlying cause of your suffering remains a mystery. "What causes a hangover? Nobody really knows," says epidemiologist Jonathan Howland. "And what can you do about it? Nobody knows."

Alcohol has long been the only recreational drug for which scientists could not articulate a mechanism of action - which is to say, no one knew how it got you drunk, and no one knew how it got you hungover. And that's weird. Because hangovers are a problem of vast proportions. By one estimate, hangovers cost $160 billion in lost revenue every year in the US alone. Yet for decades, even as scientists have written hundreds of thousands of articles about alcohol, only a tiny fraction of that attention - just a few hundred papers - have focused on the hangover. In fact, it wasn't until the past decade or so that researchers even agreed to define hangover with a common group of symptoms.

Now, though, that's all beginning to change. In the past five or six years, a small group of researchers have dedicated themselves to the hangover, peering into both its causes and the truth behind all the purported cures. They've even made some progress on a few cures of their own. Thanks to science, the morning after is finally starting to look a little less bleak.

In the mid-2000s, Howland, then a professor of community health services at the Boston University School of Public Health, partnered with Damaris Rohsenow, an alcohol and drug abuse researcher at Brown University, to look at how hangovers relate to the ability to perform a job. "We were interested not so much in hangover as a cluster of symptoms but in impairment the day after heavy drinking," Howland says.

It wasn't until 2009, though, that a Dutch researcher named Joris Verster got the world's hangover researchers together for an informal meeting. They dubbed themselves the Alcohol Hangover Research Group and adopted a whimsical logo: a red and white crest with a tipped-over wineglass in the foreground and a pint of beer in the background. (Look closely and you'll see the beer glass is decorated with the AHRG logo in miniature - just the sort of infinite recursion that would, if you had a hangover, make you vomit.)

Over the past five years, AHRG has put out research to reveal that pretty much everything anyone has ever told you about the causes of hangover is wrong - or at least unproven.

Take dehydration. Sure, it makes sense: Alcohol suppresses the antidiuretic hormone vasopressin, which ordinarily keeps you from peeing too much. Plus, if you're drinking booze, you're probably not drinking water. But in dehydrated people with hangovers, levels of electrolytes don't differ too much from baseline controls - and when they do, they don't correlate with hangover severity.

Some scientists have pointed to acetaldehyde, a demonstrably toxic byproduct of ethanol breakdown in the body. It's a nice theory - but it turns out that hangover symptoms are at their worst when acetaldehyde levels are low.

Low blood sugar is another common explanation, and it has some intuitive power behind it. Dehydration itself may not cause hangovers, but it does cause glucose levels to drop, and the body compensates by turning to other sources of energy, which can cause hangover-like symptoms. But if low blood sugar were the problem, administering glucose and fructose ought to be the solution. And it's not - sugar doesn't help the morning after. A more likely culprit is actually high blood sugar. Consuming ethanol with glucose turns out to elevate lactate levels, and one study shows that the presence of lactate makes hangovers worse. (So those warnings about sweet drinks might have something to them.)

Despite the cloud of misinformation, the AHRG has been able to pin down some basics. Get your blood alcohol concentration above 0.10 percent and odds are you'll be hungover the next day; symptoms will peak about 12 to 14 hours later, when your BAC is back at or near zero. There does also seem to be some truth to the notion that vodka delivers less of a hangover than red wine or whiskey. A comparison of people who drank enough bourbon or vodka to get to between 0.1 and 0.15 BAC - which is superdrunk, by the way - showed that all of them got hangovers, but the bourbon drinkers reported theirs as significantly worse.

Best of all, AHRG's researchers have begun to converge on a promising -theory about what really causes hangovers: namely, that they're an inflammatory response, like what happens when we get an infection. A team in Korea noticed that hangovers are accompanied by elevated levels of molecules called cytokines, which are used as communication signals by the immune system. If you inject those into a healthy subject, that person will start to have all kinds of familiar-sounding symptoms, including nausea, gastrointestinal distress, headache, chills, and fatigue. Potentially even more interesting, higher-than-normal cytokine levels also interfere with memory formation - which might account for ethanol--related lapses in recall as well.

If it's correct that cytokines are the key to hangovers, then that would suggest a simple and profound approach to treatment. That is, if the mechanism of hangover is an inflammatory response - as to a wound or illness - then maybe anti--inflammatories are the way to dispel it. (I myself now take a couple of ibuprofen before bed after a long night.)

Nobody really knows how booze works in the brain, but Richard Olsen, a neuro-scientist at UCLA who studies alcohol use, is pretty far along in figuring that out. He studies the range of blood alcohol concentrations you get from zero to a couple of drinks. In that range, he says, the neural mechanisms that respond to alcohol are very specific and present very interesting targets for treatment - of both drunkenness and hangover.

Olsen thinks the key is a neurotransmitter, a molecule that neurons use to talk to each other. Specifically, he's looking at one called gamma aminobutyric acid, or GABA. In particular, Olsen is looking at a subtype of the receptors that GABA sticks to, one that is exquisitely sensitive to ethanol. It is, Olsen says, "a unique ethanol receptor that responds to low concentrations of ethanol, as produced by one glass of wine, in the brain."

Now, GABA is an inhibitory neurotransmitter - i.e., it slows things down - so ethanol, in sparking these same receptors, would have a similar effect. That's why at lower doses it mellows you out. If Olsen's right, this could be the chemical mechanism that has eluded scientists until now. And he has some evidence: A drug that blocks those specific GABA receptors also blocks the effects of ethanol in rats. (Unfortunately that drug is in a family called the benzodiazepines - cousins of Valium - and taking it knocks you on your ass as surely as a stiff drink.) Another piece of favorable evidence: After repeated exposure to ethanol, neurons start to make a different kind of receptor, one that's more resistant to the stuff. (This has its own downside - the new receptors are also less sensitive to GABA, which means all those neurons are more difficult to inhibit generally. Parts of the brain become overexcitable, leading to tremors, almost a pre-seizure condition, and symptoms that look a lot like a hangover.)

Knowing that she was looking for a drug that would bind to that specific receptor - and nothing else - one of Olsen's postdoctoral students, a researcher named Jing Liang, started experimenting with herbs from her native China, beginning with the ones that traditional medicine claimed had an effect on alcohol. And she found one. "Hovenia," she says. "It's been used in Asia for 500 years. I found it in a grocery store."

The lab purified the plant until Olsen and his team had an ingredient that acted on the right receptor. It turned out to be a flavonoid, a common molecular family. It already had a name - ampelopsin - but they started talking about it according to the naming conventions of organic chemistry: dihydromyricetin.

"Jing gave a talk at a meeting about our results, and we invited our friends to the bar afterward to try it out," Olsen says. "Now, this is not publishable, and you can't use it for evidence for the FDA, but it's good for us to know what kind of dose we should be using in our clinical trial - and that it doesn't hurt anybody and does something to us that we want."

The people who took the pill all reported feeling less intoxicated than they would ordinarily, he says. And they felt less hungover the next day. (Scientific research conferences are famous for active bar scenes, but I assume that the ones at alcohol research meetings rage the hardest and result in the most guilt afterward.) One of Liang and Olsen's funders now sells dihydromyricetin over the counter as BluCetin. It joins an elite club of hard-to-find substances - a prickly pear extract called Opuntia ficus indica, a vitamin B6 analog called pyritinol, and a migraine drug called Clotam - that have been reliably shown to help the symptoms of a hangover.

Olsen's line of research also suggests a more radical approach to eliminating the hangover. What if our cocktails used something other than alcohol to get us tipsy? Given the seemingly analogous chemical effects of alcohol and some synthetic drugs, it's hypothetically possible to find a chemical with almost the same effects as alcohol but that's better understood and better controlled. Alcohol researchers have been looking for something like this for decades, and now a British psychiatrist named David Nutt claims to have figured it out.

For a couple of years, Nutt - who was one of the British government's top drug policy advisers until he pointed out, quite rationally, that it made no sense to regulate pot heavily and booze barely at all - has been reporting experiments on chemical analogs to ethanol that deliver the same glorious buzz but with a crucial difference: There are antidotes that instantly restore sobriety. In a paper in 2006, Nutt showed how his very Star Trek-ish synthohol would work on a particular subtype of receptors for GABA, one not entirely understood. Like the receptor that Olsen was studying, Nutt's receptors also handle benzo-diazepines, so they clearly have an impact on alertness.

Now, Nutt says, he has no less than five candidate chemicals ready to go. "After exploring one possible compound, I was quite relaxed and sleepily inebriated for an hour or so," Nutt wrote in a commentary for the Guardian in late 2013. "Then, within minutes of taking the antidote, I was up giving a lecture with no impairment whatsoever." All he needs, he says, is funding for more tests. If Nutt is right, his discovery would shed light not just on how ethanol affects the brain but how the brain works more broadly. And existence of antidotes means that all you'll need is a pill or a swig to avoid a hangover entirely. Remember to take it the night before and there will never again be a morning after. Or so we can hope.

http://www.eurekalert.org/pub_releases/2014-05/nlmc-mtt051614.php

More than two-thirds of healthy Americans are infected with human papilloma viruses

Only a few of more than 109 detected strains known to cause cancer

In what is believed to be the largest and most detailed genetic analysis of its kind, researchers at NYU Langone Medical Center and elsewhere have concluded that 69 percent of healthy American adults are infected with one or more of 109 strains of human papillomavirus (HPV). Only four of the 103 men and women whose tissue DNA was publicly available through a government database had either of the two

HPV types known to cause most cases of cervical cancer, some throat cancers, and genital warts.

Researchers say that while most of the viral strains so far appear to be harmless and can remain dormant for years, their overwhelming presence suggests a delicate balancing act for HPV infection in the body, in which many viral strains keep each other in check, preventing other strains from spreading out of control. Although infection is increasingly known to happen through skin-to-skin contact, HPV remains the most common sexually transmitted infection in the United States. It is so common that experts estimate nearly all men and women contract some strain of it during their lives.

"Our study offers initial and broad evidence of a seemingly 'normal' HPV viral biome in people that does not necessarily cause disease and that could very well mimic the highly varied bacterial environment in the body, or microbiome, which is key to maintaining good health," says senior study investigator and NYU Langone pathologist Zhiheng Pei, MD, PhD. Dr. Pei, an associate professor at NYU Langone, plans to present his team's findings on May 20 in Boston at the annual meeting of the American Society for Microbiology.

Lead study investigator and NYU Langone research scientist Yingfei Ma, PhD, says "the HPV 'community' in healthy people is surprisingly more vast and complex than previously thought, and much further monitoring and research is needed to determine how the various non-cancer-causing HPV genotypes interact with the cancer-causing strains, such as genotypes 16 and 18, and what causes these strains to trigger cancer."

For the study, which took two years to complete, researchers analyzed data made publicly available from the National Institutes of Health (NIH) Human Microbiome Project, which is gathering information on microorganisms' effects on human health.

The NIH data consisted of comprehensive DNA analyses assembled by a technique called shotgun sequencing. The DNA decoding technique helped sort through vast amounts of genetic material among 748 tissue swabs of study participants' major organs, including skin, vagina, mouth, and gut. Tissue samples were originally collected from healthy study volunteers, ages 18 to 80, participating in the NIH project. In shotgun sequencing, the genetic code of long strands of DNA is deciphered in a random firing pattern, much like pixels in a photo, until a full picture becomes apparent.

Researchers then refined their analysis to only HPV strains by removing all human DNA sequences and, using special bioinformatics software developed at NYU Langone, comparing what was left with known national databases on HPV.

Dr. Pei cautions that until the harm or benefits of the many HPV strains become apparent, people should not be overly concerned, but consult their physician or an infectious disease specialist to assess any potential threat before seeking any antiviral or other therapy. In addition, he says getting vaccinated against types 16 and 18 is still "a good idea," especially for preventing cervical cancer, until broader, more comprehensive anti-HPV vaccines become available that also target cancers in other body organs and tissues.

Among the study's other key findings:

Some 109 of 148 known HPV types were detected in study participants.

Most study participants had HPV infections in the skin (61 percent); then vagina (41 percent), mouth (30 percent), and gut (17 percent).

Of the 71 study participants infected with HPV, 42 (59 percent) had HPV in only one organ, 22 (31 percent) had it in two organs, and seven (10 percent) had it in three; none had HPV in all four organs tested.

Skin samples contained the most varied HPV strains (80 types of HPV, including 40 that were found only in the skin). Vaginal tissue had the second most numerous strains (43 types of HPV, with 20 strains exclusive to the organ), followed by mouth tissue (33 types, of which five were exclusively oral in origin), and gut tissue (six types, all of which were found in other organs).

Dr. Pei says his team's study results also highlight the weaknesses in current clinical test kits for HPV, currently designed to recognize only a dozen or more viral types most closely tied to cervical cancer. He says broader detection methods and comprehensive diagnostic tests are needed to more accurately assess people's "true" HPV infection status.

According to Dr. Ma, the team has plans to investigate which non-cancer-causing HPV types may play a role in cancers of the cervix, mouth and skin. The team also plans to develop better diagnostic tests, which would test for all known types of HPV.

Note: This poster presentation,#2357, at the American Society for Microbiology meeting is titled "Human Papillomavirus Community in Healthy Persons, Defined by Metagenomics Analysis of Human Microbiome Project Shotgun Sequencing Data Sets" and will be on display from 10:45 a.m. to 12 noon EST, Tuesday, May 20, in Exhibit Hall B at the Boston Convention Center in Boston, Mass.

Funding support for the study was provided through the US NIH Roadmap Initiative's Human Microbiome Project (grant number UH3 CA140233) and the National Cancer Institute, also a member of the NIH (grant number U01 CA18237), with additional support from the Office of Research and Development, Veterans Health Administration, at the US Department of Veterans Affairs.

In addition to Drs. Pei and Ma, NYU Langone study co-investigators included Liying Yang, MD, MSc. Research assistance was also provided by study co-investigators Ramana Madupu, PhD; Shibu Yoosef, PhD; and Karen Nelson, PhD, at the J. Craig Venter Institute in Rockville,

Md., and in San Diego, Calif.; Ulas Karaoz, PhD; and Eoin Brodie, PhD, at the Lawrence Berkeley National Laboratory in Berkeley, Calif.; Carlos Nossa, PhD, at Gene by Gene Ltd., in Houston, Texas; and Patrick Yachimski, MD, at Vanderbilt University in Nashville, Tenn.

www.eurekalert.org/pub_releases/2014-05/asfm-mf1051414.php

Microbes from 1,500-year-old feces support archeological theories

By evaluating the bacteria and fungi found in fossilized feces, microbiologists are providing evidence to help support archeologists' hypotheses regarding cultures living in the Caribbean over 1,500 years ago.

They report their findings today at the annual meeting of the American Society for Microbiology.

"Although fossilized feces (coprolites) have frequently been studied, they had never been used as tools to determine ethnicity and distinguish between two extinct cultures. By examining the DNA preserved in coprolites from two ancient indigenous cultures, our group was able to determine the bacterial and fungal populations present in each culture as well as their possible diets," says Jessica Rivera-Perez of the University of Puerto Rico, Rio Piedras, who presented the study.

This shows 1,500 year-old fossilized feces (coprolite) discovered in Vieques, Puerto Rico. "The study of the paleomicrobiome of coprolites supports the hypothesis of multiple ancestries and can provide important evidence regarding migration by ancestral cultures and populations of the Caribbean," says researcher Jessica Rivera-Perez. **Center of Archaeological Research of the University of Puerto Rico, Rio Piedras**

Various indigenous cultures inhabited the Greater Antilles thousands of years ago. The Dominican Republic and Puerto Rico have thousands of pre-Columbian indigenous settlements belonging to extinct cultures that migrated to the Caribbean at some point in history.

Archaeological excavations in Vieques, Puerto Rico unearthed hand-made tools and crafts as well as fossilized feces dating from 200 to 400 A.D. The presence of two distinct styles of craftsmanship, as well as other clues obtained from the dig sites, suggested these artifacts belonged to two distinct cultures.

"One culture excelled in the art of pottery; in fact, their signature use of red and white paint helped identify them as descendants from the Saladoids, originating in Saladero, Venezuela. In contrast, the second culture had exquisite art for crafting semiprecious stones into ornaments, some of which represented the Andean condor. This helped archaeologists identify the Bolivian Andes as possible origins of this Huecoid culture," says Rivera-Perez.

To help confirm these archeological hypotheses, Rivera-Perez and her colleagues examined the DNA preserved in coprolites from both Saladoid and Huecoid settlements and compared the bacterial and fungal populations found in each. Major differences were detected between the fecal communities of these cultures, providing additional support that they may have had different origins. Additionally, they found fungal and corn DNA in the Huecoid coprolite that suggests the consumption of an Andean fermented corn beverage, further confirming the theory that the Huecoids originated in the Bolivian Andes.

"The study of the paleomicrobiome of coprolites supports the hypothesis of multiple ancestries and can provide important evidence regarding migration by ancestral cultures and populations of the Caribbean," says Rivera-Perez.

This study was conducted by collaborators from the University of Puerto Rico and California Polytechnic State University, San Luis Obispo. This study was partially funded by the NIH Grant to the University of Puerto Rico (Research Initiative for Scientific Enhancement Program).

http://bit.ly/1gZmahR

Biotech Factories to Farm Fake Meat

Village-level "meat factories" would produce unique flavors of artificial beef, pork or chicken

May 20, 2014 12:45 PM ET // by Eric Niiler

The movement to sell locally sourced, artisanal food and drink has picked up steam in recent years as many consumers demand better quality products with a smaller environmental footprint and traceable pedigree. But some Dutch researchers are taking this idea a step further, proposing the creation of village-level "meat factories" that would produce unique flavors of artificial beef, pork or chicken, all from a biotech reactor.

The study builds upon work done last year, the so-called "test-tube hamburger" that was created by researchers at the University of Maastrict in the Netherlands and unveiled at a tasting in London.

There's nothing quite like a juicy steak straight off the grill, but scientists are coming close to replicating that meaty greatness, without the meat! Annie sinks her teeth into the advances in fake meat.

This latest study by a pair of researchers at Wagenigen University proposes a device that can create meat cells in a metal container – enough to feed a small amount of "cultured beef" each month to a village of 2,650 people.

"We thought it was interesting and most promising to do cultured meat on a small scale," said Cor van der Weele, professor of philosophy who wrote the paper with biotechnology professor Johannes Tamper in the journal Trends in Biotechnology. "A small scale is also good from a biotechnology point of view."

Van der Weele said she was inspired to come up with this alternative to meat because of her concerns over animal welfare, as well as the environmental impact of land used to grow beef cattle. “Raising small numbers of animals in a village is fine,” Van der Weele said. “But the way animals are raised now is not in small amounts but in large scale and factory farms.”

The process extracts stem cells from muscle tissue of cows, pigs or chickens, and culturing them in a 20 meter-squared bioreactor. The number of cells would grow exponentially as long as the liquid culture medium can be kept sterile, according to the study. The reactor would produce 22 pounds of meat per person per year, enough to reduce, but not eliminate, demand for other sources of animal protein. Villages could tweak the meat to capture their own local flavors, or “terroir,” according to Van der Weele.

The Dutch researchers admit the biggest obstacle is cost. Last year’s in vitro burger cost $325,000 and any village-level bioreactor would need an expensive growth medium, pushing the cost to about $240 per pound of meat.

Top 5 Scariest Bioweapons: Photos

“From a technological perspective, ‘village-scale’ production is also a promising option,” the authors wrote. “From an economic point of view, however, competition with ‘normal’ meat is a big challenge; production cost emerges as the real problem. For cultured meat to become competitive, the price of conventional meat must increase greatly.”

Warren Ruder, assistant professor of biological systems engineering at Virginia Tech, agreed that the technology is already there to build bio-beef, it just cost a lot. “The type of culture they are describing is relatively simple,” Ruder said. “We’ve been making artificial muscle in the laboratory for a decade.”

Cost isn’t the only issue. Some critics wonder if people would really eat it. Last year’s burger was flavored with salt, egg powder, breadcrumbs, with beet juice and saffron for color. “My gut reaction is lot of folks would have the same general feeling that I do,” said Chase Adams, a spokesman for the National Cattleman’s Beef Council in Washington, DC. “I don’t think it’s overly palatable.”

www.bbc.com/news/health-27482574

Chronic pain 'may be inherited'

Four common chronic pain conditions share a genetic element, suggesting they could - at least in part - be inherited diseases, say UK researchers.

The four include irritable bowel syndrome, musculoskeletal pain, pelvic pain and dry eye disease. The study of more than 8,000 sets of twins found the ailments were common in identical pairs sharing the same DNA. The King's College London team say the discovery could ultimately help with managing these debilitating diseases. While environmental factors probably still play a role in the four conditions, genes could account for as much as two-thirds of someone's chances of developing the disease, they believe. They told the journal Pain that more research is needed to pinpoint the precise genes involved.

'Life-changing'

Chronic pain - pain which persists or recurs for months on end - is common and has many different causes, which can make it difficult to diagnose and treat. While the pain can be related to other medical conditions, it is thought to be caused by problems with the nervous system, sending pain signals to the brain despite no obvious tissue damage. Experts are keen to understand more about chronic pain to improve the quality of life of the millions of people who have to endure it.

Some have suspected that some people may have a genetic predisposition to chronic pain since many sufferers share similar symptoms and often have more than one of the different types of chronic pain conditions.

The team at King's College London decided to study identical and non-identical twins because these two groups provide an ideal comparison for investigating inherited genes - identical twins share the same DNA while non-identical twins do not.

Lead investigator Dr Frances Williams said: "This study is one of the first to examine the role of genetic and environmental factors in explaining the links between different chronic pain syndromes. The findings have clearly suggested that chronic pain may be heritable within families. With further research, these findings could then lead to therapies which may change the lives of those suffering with chronic pain."

http://phys.org/news/2014-05-bacteria-species-curiosity-baggage-mars.html

Bacteria species part of Curiosity baggage on Mars

When the Curiosity rover landed on Mars in 2012, there may have been dozens of microbial species, having withstood pre-launch spacecraft cleaning.

Phys.org - This is the finding of a study titled "Identification and Survival of Isolates Collected from the Mars Rover, Curiosity." The scientists who worked on the study, from the University of Idaho, Jet Propulsion Lab at CalTech in Pasadena, Idaho State University, South Dakota School of Mines and Technology, and Colby College, presented their findings on Monday to the American Society for Microbiology meeting in Boston.

Reporting on this project, Nature News said their study is the first to examine the entire archive of microbes collected from Curiosity. The study is not only interesting for the number of strains identified but also for observations about their resistance. Results from the study can now provide details about the microbes that inhabit the surfaces of spacecraft after microbial reduction.

Nature News, commenting on the findings, referred to "a surprising number" resisting extreme temperatures and damage caused by ultraviolet-C radiation, the most potentially harmful type.

In their presentation abstract, the authors explained how organisms were collected during MSL's planetary protection implementation campaign. (MSL refers to the Mars Science Laboratory.). Isolates were identified and characterized using standard culturing and molecular techniques. Results showed 62% of the 377 organisms identified were related to members of the Bacillus genus while 31% belonged to non-spore-forming genera. Many isolates showed resistance to desiccation (78%), and UVC radiation and 94% of the isolates could grow in the presence of elevated salt conditions (≥10% NaCl) and 35% at low temperatures (4C), while 11% of isolates could survive under multiple extreme conditions.

The authors' comments reflect a concern among scientists over contamination, as they said that "this study will help gauge whether microorganisms from Earth pose a forward contamination risk that could impact future life detection and sample return missions. The overall outcome of this study will provide knowledge about the hardiest of organisms on the spacecraft and could benefit the development of cleaning and sterilization technologies to prevent forward contamination."

A Scientific American article in 2011 also noted why scientists are concerned about cleanliness standards: "Adhering to cleanliness standards is a way to make sure the mission does not transport Earth life to Mars. Doing so preserves the ability to study that world in its natural state and also avoids contamination that would obscure an ability to find native life on that planet, if it exists."

http://bit.ly/1jOwwRH

Can Acupuncture Curb Killer Immune Reactions?

A needle-based technique has been shown to switch on nerves that tamp down sepsis

May 1, 2014 |By Gary Stix

The ST36 Zusanli acupuncture point is located just below the knee joint. This spot in mice—and it is hoped perhaps in humans—may be a critical entryway to gaining control over the often fatal inflammatory reactions that accompany systemic infections. Sepsis kills as many as 250,000 patients in the U.S. every year, some 9 percent of overall deaths. Antibiotics can control sepsis-related infection, but no current drugs have fda approval for counteracting the runaway immune response.

Researchers at Rutgers University New Jersey Medical School reported online in Nature Medicine on February 23 that stimulating ST36 Zusanli with an electric current passed through an acupuncture needle activated two nerve tracts in mice that led to the production of a biochemical that quieted a sepsislike inflammatory reaction induced in mice. (Scientific American Mind is part of Nature Publishing Group.)

The finding, which also involved the collaboration of the National Medical Center Siglo XXI in Mexico City and other institutions, raises the possibility that knowledge derived from alternative medicine may provide a means of discovering new nerve pathways that can regulate a variety of immune disorders, from rheumatoid arthritis to Crohn's disease. If future studies achieve similar results, acupuncture might be integrated into the nascent field of bioelectronics medicine—also called electroceuticals—that is generating intense interest among both academics and drug companies.

Clues from Acupuncture

Luis Ulloa, who headed the study at the Center for Immunity and Inflammation at Rutgers, has spent more than 10 years researching how nerve signals control immune function. Following the suggestion of a Mexican colleague, he realized that it might be worth testing whether acupuncture could help discover some of these much sought neuroimmune pathways.

Ulloa and his team used electroacupuncture to stimulate the ST36 Zusanli acupuncture point in 20 mice exposed to lipids and carbohydrates from the outer membrane of bacteria, producing an inflammatory response that mimics sepsis. Another 20 rodents received “sham” electroacupuncture in which nonacupuncture points were stimulated. Half of the mice in the first group survived, whereas all the sham-treated rodents perished. A similar survival difference was noted with two groups of mice exposed to a cocktail of microbes in the gut.

Researchers then began to analyze the nerves and organs involved. They traced a pathway beginning in a branch of the sciatic nerve, not far from ST36 Zusanli, that relayed a signal to the spinal cord and then the brain. Once processed there, it was sent down to the vagus nerve, finally reaching the adrenal glands, which produced the key anti-inflammatory agent, the neurotransmitter dopamine. Ulloa's team set about confirming the parts of this biological wiring diagram by removing independently sections of the key nerves and the entire adrenal glands. Excision of any one of these links in this newly discovered neuroimmune circuit abolished electroacupuncture's anti-inflammatory effects.

The researchers also succeeded in quelling inflammation by using a drug called fenoldopam (Corlopam), which acted as a stand-in for the adrenal-produced dopamine in mice who had the glands surgically removed. Having a drug at hand might be essential because the adrenals in many sepsis patients function poorly, which makes them unsuitable candidates for acupuncture therapy.

The Rutgers work with acupuncture might be a relatively noninvasive means of performing neuroimmune stimulation and researching the interaction between the

nervous and immune systems. “There are hundreds of these [neuroimmune] circuits that haven't been mapped, and some of them may map to acupuncture points,” says Kevin Tracey of the Feinstein Institute for Medical Research on Long Island, who is one of the pioneers of bioelectronic medicine.

Tracey, a former colleague of Ulloa's, adds that studies such as the one from the Rutgers group could help establish a physiological mechanism to explain why acupuncture might work as a treatment. Tracey's own research led to the founding of a company called SetPoint Medical in Valencia, Calif., which is developing an implantable device to activate a separate neuroimmune pathway to treat inflammatory diseases.

Testing Ancient Treatments

Acupuncture still has its critics at various ends of the medical spectrum. Some acupuncture proponents perceive a study on sepsis as a case of Western medicine finally conferring a belated blessing on techniques that have been accepted treatments for thousands of years. Skeptics of alternative medicine, meanwhile, criticize any investigation of acupuncture as a waste of limited research dollars on a folk remedy for which a firm scientific basis will never be found.

Steven Novella, president of the New England Skeptical Society, characterizes the sepsis study as having merely shown that a nerve responds to the application of an electric current. “Electroacupuncture itself is not a real entity, in my opinion,” he says. “It is just electrical stimulation. Doing stimulation through an ‘acupuncture needle’ is meaningless—it's just a thin needle. There's nothing that makes it an acupuncture needle. And there is no evidence that acupuncture points exist at all.”

For his part, Ulloa had no intention of trying to determine whether flows of vital energy, or qi, were making their way through the body's “meridians” based on the interpretation for how acupuncture works in Chinese traditional medicine. In fact, he agrees with Novella's argument about nerve stimulation. In the study, the researchers found no anti-inflammatory effect when a toothpick was used to probe ST36 Zusanli, in a manner similar to the way acupuncture needles had been inserted for centuries before the advent of electroacupuncture.

As a prospector for neuroimmune pathways, Ulloa insists his interest in exploring acupoints in his research has not flagged. “It is no coincidence that all acupoints but one—360 of 361 described in humans—are located in the proximity of a major nerve,” Ulloa says. In his study, ST36 Zusanli led directly to the discovery of one of the most intricate neuroimmune circuits found to date. “Instead of testing millions of potential points, we reasoned that acupoints may provide an advantage in stimulating neuronal networks more efficiently,” he says.

A few days after the acupuncture paper in Nature Medicine appeared, a study published in Science Translational Medicine documented that a component of the herb Salvia miltiorrhiza, another hand-me-down from the Chinese traditional medicine pharmacopeia, also turned out to have potent anti-inflammatory properties. The researchers from leading institutions who wrote that paper were taking the same path as Ulloa and his team, attempting to test whether an ancient treatment had through trial and error turned up some biological effect or therapeutic potential that could be subject to a rigorous testing regimen in the laboratory.

In both reports, the authors were following the dictates that top-flight journal editors, article reviewers—and the skeptics themselves—endorse for evidence-based medicine. This type of study will certainly be more the exception than the rule. These same journals will never be publishing on feng shui and homeopathy—and the acupuncture entries in their pages will still be relatively scarce. But if scientists studying acupuncture or herbs can cross the high bars set by the scientific establishment, what's wrong with that?

http://www.eurekalert.org/pub_releases/2014-05/bu-ngq051414.php

Neuroscience's grand question

A new model to understand neural self-regulation

When your car needs a new spark plug, you take it to a shop where it sits, out of commission, until the repair is finished. But what if your car could replace its own spark plug while speeding down the Mass Pike?

Of course, cars can't do that, but our nervous system does the equivalent, rebuilding itself continually while maintaining full function.

Neurons live for many years but their components, the proteins and molecules that make up the cell are continually being replaced. How this continuous rebuilding takes place without affecting our ability to think, remember, learn or otherwise experience the world is one of neuroscience's biggest questions.

And it's one that has long intrigued Eve Marder, the Victor and Gwendolyn Beinfield Professor of Neuroscience. As reported in Neuron on May 21, Marder's lab has built a new theoretical model to understand how cells monitor and self-regulate their properties in the face of continual turnover of cellular components.

Ion channels, the molecular gates on the surface of cells, determine neuronal properties needed to regulate everything from the size and speed of limb movement to how sensory information is processed. Different combinations of types of ion channels are found in each kind of neuron. Receptors are the molecular 'microphones' that enable neurons to communicate with each other.

Receptors and ion channels are constantly turning over, so cells need to regulate the rate at which they are replaced in a way that avoids disrupting normal nervous system function. Scientists have considered the idea of a 'factory' or 'default' setting for the numbers of ion channels and receptors in each neuron. But this idea seems

implausible because there is so much change in a neuron's environment over the course of its life.

If there is no factory setting, then neurons need an internal gauge to monitor electrical activity and adjust ion channel expression accordingly, the team asserts. Because a single neuron is always part of a larger circuit, it also needs to do this while maintaining homeostasis across the nervous system.

The Marder lab built a new theoretical model of ion channel regulation based on the concept of an internal monitoring system. The team, comprised of postdoctoral fellow Timothy O'Leary, lab technician Alex Williams, Alessio Franci, of the University of Liege in Belgium, and Marder, discovered that cells don't need to measure every detail of activity to keep the system functioning. In fact, too much detail can derail the process.

"Certain target properties can contradict each other," O'Leary says. "You would not set your air conditioning to 64 degrees and your heat to 77 degrees. One might win over the other but they would be continually fighting each other and you would end up paying a big energy bill."

The team also learned that cells can have similar properties but different ion channel expression rates - like cellular homophones, they sound alike but look very different. The model showed that the very internal monitoring system designed to control runaway electrical activity can actually lead to neuronal hyperexcitability, the basis of seizures. Even if set points are maintained in single neurons, overall homeostasis in the system can be lost.

The study represents an important advance in understanding the most complex machinery ever built — the human brain. And it may lead to entirely different therapeutic strategies for treating diseases, O'Leary says. "To understand and cure some diseases, we need to pick apart and understand how biological systems control their internal properties when they are in a normal healthy state, and this model could help researchers do that."

This research was funded by the National Institute of Health and the Charles A. King Trust.

http://www.eurekalert.org/pub_releases/2014-05/sri-sfa052114.php

Scientists find an unlikely stress responder may protect against Alzheimer's

The findings point to new approach to Alzheimer's prevention and therapy

La Jolla, Ca - In surprise findings, scientists at The Scripps Research Institute (TSRI) have discovered that a protein with a propensity to form harmful aggregates in the body when produced in the liver protects against Alzheimer's disease aggregates when it is produced in the brain. The results suggest that drugs that can boost the protein's production specifically in neurons could one day help ward off Alzheimer's disease.

"This result was completely unexpected when we started this research," said TSRI Professor Joel N. Buxbaum, MD. "But now we realize that it could indicate a new approach for Alzheimer's prevention and therapy." Buxbaum and members of his laboratory report their latest finding in the May 21, 2014 issue of the Journal of Neuroscience.

First Hints

The study centers on transthyretin (TTR), a protein that is known to function as a transporter, carrying the thyroid hormone thyroxine and vitamin A through the bloodstream and cerebrospinal fluid. To do this job, it must come together in a four subunit structure called a tetramer. Certain factors such as old age and TTR gene mutations can make these tetramers prone to fall apart and misfold into tough aggregates called amyloids. TTR amyloids accumulate in the heart, kidneys, peripheral nerves and other tissues and cause life-shortening diseases including familial amyloid polyneuropathy and senile systemic (cardiac) amyloidosis.

Starting in the mid 1990s, however, reports from several laboratories hinted that TTR in the brain might protect against other amyloids—particularly the Alzheimer's-associated protein amyloid beta. In test tube experiments, TTR seemed able to grab hold of amyloid beta and prevent it from aggregating. In transgenic "Alzheimer's mice," which overproduce amyloid beta, TTR expression was increased in affected brain tissue, compared to control mice, as one would expect from a protective response.

"I didn't really believe those reports at the time," Buxbaum said.

But he was working on TTR amyloidoses and had the tools needed to investigate the issue genetically. He and his colleagues at TSRI did those experiments, and found, to their surprise, that overproducing TTR in "Alzheimer's mice" did indeed protect the animals: it reduced their memory deficits as well as the accumulations of amyloid beta aggregates in their brains. Since that 2008 study, Buxbaum and colleagues have gone on to publish additional experiments examining the mechanism of the protection including two last year, in collaboration with the Wright and Kelly laboratories at TSRI and Roberta Cascella in Florence, that showed how TTR tetramers can bind to amyloid beta and inhibit the latter from forming the more harmful types of aggregate.

Context Is Everything

In the latest study, Buxbaum and his team, including lead authors Xin Wang and Francesca Cattaneo, at the time both postdoctoral fellows in the Buxbaum laboratory, found another key piece of evidence for TTR's protective role.

TTR is known to be produced principally in the liver and in the parts of the brain where cerebrospinal fluid is made. Prior studies in the Buxbaum group found evidence that TTR can also be produced in neurons, albeit at low levels. Still, it has

remained unclear how TTR production, in neurons or in other cells, would be increased in response to amyloid beta accumulation.

To start, the team analyzed a segment of DNA near the TTR gene called the promoter region, where, in principle, special DNA-binding proteins called transcription factors could increase TTR gene activity. The analysis suggested that Heat Shock Factor 1 (HSF1), known as a master switch for a broad protective response against certain types of cellular stress, could bind to the TTR gene's promoter.

Further experiments showed that HSF1 does indeed bind to this region and that two known stimulators of HSF1—heat and a compound called celastrol—also boost HSF1 binding to the TTR promoter, in addition to boosting TTR production.

Remarkably, though, the researchers found that HSF1's dialing-up of TTR production seemed to occur only in neuronal-type cells, not in liver cells where most TTR is produced.

In fact, the researchers found that in liver cells the HSF1 response somehow brought about a modest decrease in TTR production. That result may seem puzzling, but it is consistent with the idea that liver-cell TTR, which is produced at 15 to 20 times the levels of neuronal TTR, is more likely to be hazardous than protective.

Using genetic techniques to force cells to overproduce HSF1, the researchers again saw jumps in TTR gene activity and protein production, but only in neuronal cells. In liver cells TTR activity rose when HSF1 was blocked, suggesting that HSF1 normally helps keep a lid on liver TTR production.

"It's becoming more and more evident in biology that the same molecule can do very different things in different contexts," Buxbaum said.

To underscore the relevance to Alzheimer's, his team examined neurons from the hippocampus brain region in ordinary lab mice and in amyloid-beta-overproducing Alzheimer's mice. Again consistent with the concept of TTR as protective in neurons, they found that the frequency of HSF1 binding to the TTR gene promoter, and the numbers of resulting TTR gene transcripts, were both doubled in the Alzheimer's mice compared to the ordinary lab mice.

Buxbaum and his colleagues plan to do further research on this apparent TTR-mediated stress response in neurons to determine, among other things, precisely how Alzheimer's-associated amyloid beta switches it on. But they have already begun to think about developing a small molecule compound, suitable for delivery in a pill, that at least modestly boosts HSF1 activity and/or TTR production in neurons—and thus might prevent or delay Alzheimer's dementia.

Other contributors to the study, "The Systemic Amyloid Precursor Transthyretin (TTR) Behaves as a Neuronal Stress Protein Regulated by HSF1 in SH-SY5Y Human Neuroblastoma Cells and APP23 Alzheimer's Disease Model Mice," were Lisa Ryno, John Hulleman and Natàlia Reixach, all of TSRI at the time of the study. See http://www.jneurosci.org/content/34/21/7253.abstract

The study was funded in part by the National Institutes of Health (AGR01030027).

http://www.eurekalert.org/pub_releases/2014-05/uomh-mww051914.php

Most women who have double mastectomy don't need it, U-M study finds

Worry about recurrence was driving factor, but 70 percent had very low risk of developing cancer in healthy breast

ANN ARBOR, Mich. - About 70 percent of women who have both breasts removed following a breast cancer diagnosis do so despite a very low risk of facing cancer in the healthy breast, new research from the University of Michigan Comprehensive Cancer Center finds.

Recent studies have shown an increase in women with breast cancer choosing this more aggressive surgery, called contralateral prophylactic mastectomy, which raises the question of potential overtreatment among these patients.

The study authors looked at 1,447 women who had been treated for breast cancer and who had not had a recurrence. They found that 8 percent of women had a double mastectomy, and that 18 percent considered having one. Results appear in JAMA Surgery.

Overall, about three-quarters of patients reported being very worried about their cancer recurring. Those who chose to have both breasts removed were significantly more likely to express concern about recurrence. But, a diagnosis of breast cancer in one breast does not increase the likelihood of breast cancer recurring in the other breast for most women.

"Women appear to be using worry over cancer recurrence to choose contralateral prophylactic mastectomy. This does not make sense, because having a non-affected breast removed will not reduce the risk of recurrence in the affected breast," says Sarah Hawley, Ph.D., associate professor of internal medicine at the U-M Medical School.

In addition to asking about the type of treatment, researchers asked about clinical indications for double mastectomy, including the patients' family history of breast and ovarian cancer and the results of any genetic testing.

Women with a family history of breast or ovarian cancer or with a positive genetic test for mutations in the BRCA1 or BRCA2 genes may be advised to consider having both breasts removed, because they are at high risk of a new cancer developing in the other breast. This represents about 10 percent of all women diagnosed with breast cancer. Women without these indications are very unlikely to develop a second cancer in the healthy breast.

The study found that among women receiving a double mastectomy, nearly 70 percent did not have either a family history or positive genetic test. Many of these women were candidates for breast-conserving lumpectomy.

"For women who do not have a strong family history or a genetic finding, we would argue it's probably not appropriate to get the unaffected breast removed," says Hawley, who is also a research investigator at the Ann Arbor VA Center of Excellence in Clinical Care Management Research and a member of the U-M Institute for Healthcare Policy and Innovation.

A double mastectomy is a bigger operation that is associated with more complications and a more difficult recovery. In addition, most women went on to have breast reconstruction as well. Women might also still need to undergo chemotherapy or radiation therapy after their surgery – treatments that are known to reduce the risk of cancer recurring – which could delay their recovery further.

The study also found that women with higher education levels and women who had undergone an MRI test before surgery were more likely to choose double mastectomy. Concern about recurrence was one of the biggest factors driving the decision to have this surgery.

The researchers say it's important to educate women better about the risks and benefits of contralateral prophylactic mastectomy, but that surgeons must also be aware of how patients' worry about recurrence drives their decision-making.

Breast cancer statistics: 235,030 Americans will be diagnosed with breast cancer this year and 40,430 will die from the disease, according to the American Cancer Society

Additional authors: Reshma Jagsi, Nancy K. Janz, Steven J. Katz, University of Michigan; Monica Morrow, Memorial Sloan-Kettering Cancer Center; Ann Hamilton, University of Southern California; John J. Graff, Rutgers Cancer Institute

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http://phys.org/news/2014-05-fossil-discovery-alps-theory-deep.htm

Fossil discovery in Alps challenges theory that all deep sea animals evolved from shallow water ancestors

New archeological evidence suggests not all deep sea creatures evolved in shallow waters and then moved deeper

Phys.org - A team of researchers with members from several European countries has published a paper in the journal Proceedings of the Royal Society B: Biological Sciences, arguing that new archeological evidence suggests not all deep sea creatures evolved in shallow waters and then moved deeper. Fossil discoveries in the Austrian Alps, they claim, offer evidence that some deep sea creatures actually evolved in the deep sea and are the ancestors of many modern deep sea creatures.

For most of modern science, ocean scientists have believed that the open ocean is a near desert, with few living creatures in it. Because of that, the consensus has been that most of the animals that do live in the deep sea today, likely evolved in shallow waters and then migrated there over millions of years. In this new effort, the researchers report on an excavation in the Austrian Alps that has yielded many fossils from ancient deep sea animals.

The team has thus far found over 2,500 fossils which have been identified as deep sea animal remains because they were clearly sea dwellers that were not light dependant. Also the rock in which they were found was similar to rock on ocean seafloors. Closer analysis of the fossils dates them back approximately 180 million years. Prior discoveries of ancient sea creature remains had been found in shallow waters, which was another reason scientists have believed deep sea creatures evolved from shallow water creatures. But the new fossil find predates any other existing find by 25 million years, suggesting they evolved from a deep sea ancestor.

In comparing the deep sea fossils with fossils from shallow living creatures from the same time frame, the researchers made another discovery. The deep sea appeared to have more biodiversity millions of years ago, than more shallow waters, turning conventional thinking on its head.

The findings by the team add more credence to the more recent view that areas of the deep sea actually have some of the highest levels of biodiversity on the planet. But, they caution, such conclusions should not imply that the deep sea may be better able to withstand changes wrought by us humans, because no one really knows if that is true or not.

More information: First glimpse into Lower Jurassic deep-sea biodiversity: in situ diversification and resilience against extinction, Published 21 May 2014 DOI: 10.1098/rspb.2013.2624

http://bit.ly/1pmoSNG

Alien Life Discovery Could Happen Within 20 Years

Curious about whether there is life beyond Earth?

May 21, 2014 03:15 PM ET // by Irene Klotz

The answer should come within 20 years, astronomers told members of a Congressional science committee on Wednesday.

A three-way race is under way to learn if life exists elsewhere in the solar system or beyond, Seth Shostak, senior astronomer with the California-based SETI Institute, said during a hearing before the House Science and Technology Committee.

So far, most efforts -- and funding -- to find extraterrestrial life have focused on Mars and potential life-bearing moons in the outer solar system.

"At least a half-dozen other worlds (besides Earth) that might have life are in our solar system. The chances of finding it, I think, are good, and if that happens, it'll happen in the next 20 years, depending on the financing," Shostak said.

A second initiative scans the atmospheres of distant planets for telltale signs of oxygen or methane, gases which, on Earth, are mostly tied to life. These searches likewise could yield results in the next two decades, Shostak added.

The third project hunts for technologically advanced aliens that are sending radio or other signals out into space. The idea behind the Search of Extraterrestrial Intelligence, or SETI, is to eavesdrop on signals that are deliberately or accidentally leaked from another world.

"That makes sense because in fact even we, only 100 years after ... the invention of practical radio, already have the technology that would allow us to send bits of information across light years of distance to putative extraterrestrials," Shostak said.

Humans' first television broadcasts, including "I Love Lucy," and "The Ed Sullivan Show," have passed 10,000 stars, noted SETI hunter Dan Werthimer, with the University of California, Berkeley.

"The nearby stars have seen 'The Simpsons.' If we're broadcasting, maybe other civilizations are sending signals in our direction -- either leaking signals the way that we unintentionally send off signals, or maybe a deliberate signal," Werthimer told legislators. "The fact that we haven't found anything means nothing," Shostak added. "We've only just begun to search."

Though there is no proof of any life beyond Earth, circumstantial evidence is mounting. Results from NASA's Kepler space telescope and other hunts for planets beyond the solar system have shown that at least 70 percent of the 200 billion to 400 billion stars in the Milky Way have planets, many well-positioned for liquid water, which is believed to be necessary for life.

More recent results from the ongoing Curiosity rover mission on Mars proved there are habitats beyond Earth suitable for microbial life.

"In our own galaxy there are tens of billions of other planets that are the kind you might want to build condos on," Shostak said. "And if that isn't adequate for your requirements, let me point out there are 150 other galaxies we can see with our telescopes, each with a similar complement of Earth-like worlds.

"What that means is that the numbers are so astounding that if this is the only planet in which not only life, but intelligent life, has arisen, then we are extraordinarily exceptional. It's like buying trillions of lottery tickets and none of them is a winner. That would be very, very unusual," Shostak said.

"The history of astronomy shows that every time we thought we were special we were wrong," he added.

http://phys.org/news/2014-05-aliens-sea-insight-evolution.html

'Aliens of sea' provide new insight into evolution

Exotic sea creatures called comb jellies may reshape how scientists view early evolution—as their genes suggest nature created more than one way to make a nervous system.

This handout photo from the University of Florida is a composite showing different views of a comb jelly known as Pleurobrachia bachei as it swims. University of Florida researchers investigated the genes of this and other comb jelly species, and found the mysterious creatures evolved a unique nervous system in a different way than other animals. **(AP Photo/University of Florida)**

These beautiful but little-known translucent animals often are called "aliens of the sea," for good reason. Somehow, they rapidly regenerate lost body parts. Some even can regrow a very rudimentary brain.

Now in an in-depth look at the genes of 10 comb jelly species, researchers report that these mysterious creatures evolved a unique nervous system in a completely different way than the rest of the animal kingdom.

In other words, the nervous system evolved more than once, a finding published Wednesday by the journal Nature that challenges long-standing theories about animal development.

"This paper proves, on a genomic basis, they're truly aliens," said University of Florida neurobiologist Leonid Moroz, whose team spent seven years unraveling the genetics behind comb jellies' neural programming.

But the findings aren't just about evolutionary history.

omb jellies build a nervous system essentially using their own biological language, Moroz explained. That points to new ways to investigate brain diseases such as Alzheimer's or Parkinson's—maybe even, one day, the ability to engineer new neurons, Moroz said.

They "open to us completely unexpected windows," he said.

Moroz is exploring some of those windows using a unique floating laboratory that allows sophisticated genomic sequencing at sea. In a test run off the coast of

Florida this spring, The Associated Press documented how his team is studying which genes switch on and off as iridescent comb jellies regenerate from injury.

All animals evolved from a single ancestor. Scientists want to determine which branches broke off first, and how the earliest animals gradually changed to become more complex. The general theory: The oldest animals were the simplest, and once neural systems emerged, they evolved in a straightforward path from primitive nerve nets up to complex human brains.

Moroz's team offered a dramatically different explanation.

The researchers mapped the full genetic code of the Pacific sea gooseberry, the nickname for a comb jelly species known as Pleurobrachia bachei. They also decoded gene activity of nine additional species of ctenophores—the scientific name for comb jellies. (The "c" is silent.)

First, they found comb jellies represent the oldest branch of the animal family tree—not the simpler sea sponges traditionally thought to hold that spot, the team reported.

That bolsters a similar finding published last December by competing scientists from the National Institutes of Health, which had been greeted with some skepticism. And it's important in this context because sponges don't have neurons. So what happened?

Parallel evolution, Moroz proposed: While other branches of the animal family tree shared one path, the comb jellies essentially went down another street as they developed circuits of neurons, nerve cells that control such functions as motion and behavior.

They simply don't have many of the genes that other animals use for neural development and function. The results were "really weird," Moroz said.

"Everybody from jellyfish to us have the same alphabet" when neurons communicate—but not the more ancient comb jellies.

For example, ctenophores don't use serotonin, dopamine and other common signaling chemicals, called neurotransmitters. Instead, they use methods unique to them.

"They're presenting data that's quite powerful," said biologist Antonis Rokas of Vanderbilt University, who wasn't part of the new work.

"It's almost like evolution has given us two different blueprints for building a structure that's very important," he added. "If your goal is to make a nervous system, it doesn't matter what the parts are in some ways. You could potentially mix and match. The more parts you have, the more solutions."

More information: The ctenophore genome and the evolutionary origins of neural systems, Nature, 2014. DOI: 10.1038/nature13400

http://www.eurekalert.org/pub_releases/2014-05/uoc--doh051914.php

Discovery of how Taxol works could lead to better anticancer drugs

Extremely subtle effect that the prescription drug Taxol has inside cells that makes it one of the most widely used anticancer agents

Drug interferes with compaction of microtubule polymer, preventing it from

University of California, Berkeley, scientists have discovered the extremely subtle effect that the prescription drug Taxol has inside cells that makes it one of the most widely used anticancer agents in the world.

The details, involving the drug's interference with the normal function of microtubules, part of the cell's skeleton, could help in designing better anticancer drugs, or in improving Taxol and other drugs already known to disrupt the workings of microtubules.

The findings are being reported in the May 22 issue of the journal Cell.

"Efforts towards understanding these chemotherapeutics better are very important, because there are some microtubule differences in cancer cells versus normal cells that maybe we can exploit," said principle author Eva Nogales, a biophysicist, UC Berkeley professor of molecular and cell biology and senior faculty scientist at Lawrence Berkeley National Laboratory (LBNL). "We are not there yet, but this is the kind of analysis we need to get there."

Taxol, originally extracted from the bark of the Pacific yew tree, is one of the mostly commonly used drugs against solid tumors, and is a front-line drug for treating ovarian and advanced breast cancer. The drug is known to bind to microtubules and essentially freeze them in place, which prevents them from separating the chromosomes when a cell divides. This kills dividing cells, in particular cancer cells, which are known for rapid proliferation.

Nogales, a Howard Hughes Medical Institute investigator, has worked on microtubules since she was a doctoral student in England in the early '90s, using techniques such as X-ray scattering and cryoelectron microscopy to study how Taxol and other anticancer agents affect microtubules. Later, during her postdoctoral work at LBNL with Ken Downing, she was the first to discover exactly where Taxol binds the basic building block, called tubulin, of the microtubule polymer.

Microtubules are the cell's skeleton

Work by many scientists around the world has shown the microtubule network inside cells, called the cytoskeleton, to be very different from rigid animal skeletons. Microtubules are polymer filaments that constantly grow and shrink, and in doing so push and pull things around the cell, including the chromosomes. Scientists call this dynamic instability. The microtubules also provide a highway for transporting the cell's organelles and other packages around the cell.

Tubulin, the basic structural unit of the microtubule, is a complex of two proteins – alpha and beta tubulin. Tubulin units stack one atop another to form strips that align with other strips and then zip up to form a hollow tube, the microtubule.

"Tubulin, the cytoskeletal protein that self-assembles into microtubules, is absolutely essential for the life of every eukaryotic cell, which is why it has become a major target of anticancer agents," Nogales said. "It's amazing how microtubules probe and try new things almost at random, but there is a level of control built into the cell that ultimately makes sense of this chaos, and the cell survives and prospers."

Microtubules grow from their free end at about 1 micron per minute by continually adding more tubulin (around 20 tubulin molecules per second). But if they stop growing, they rapidly peel apart like the skin of a banana, releasing tubulin for recycling into other microtubules. This peeling, or depolymerization, takes place at up to 15 microns per minute, or about 300 tubulin molecules falling off per second, Nogales said.

Microtubules are like compressed springs

Nogales has now discovered why microtubules peel apart so rapidly. When they assemble, the strips of tubulin are put under intense strain, but prevented from bending and pulling apart by the growing cap of tubulin on the end. Once growing stops and that cap disappears, the restrained tension rips the microtubule apart.

The tension is created when the tubulin complex, which has a small energy molecule called GTP (guanosine triphosphate) attached, becomes hydrolyzed and the GTP turns into GDP (guanosine diphosphate). This chemical reaction compacts the alpha and beta subunits, much like compacted vertebrae, keeping the tubulin stack under tension as long as the microtubule is growing at its end.

"It had been proposed that tubulin had to be constrained, but no one had proved it," Nogales said. "What we have seen is that as GTP hydrolysis happens, the tubulin structure gets stuck in a strained state, like a compressed spring. The end subunits are holding the whole thing together."

When growth stops, the tension is unleashed, and the strips peel apart rapidly.

"This work represents a major step forward on a problem with a long history," wrote Tim Mitchison in a commentary in the same issue of Cell. Mitchison, a Harvard University professor of systems biology, was the first to show the importance of GTP hydrolysis in destabilizing microtubules. The model proposed by Nogales and her team, he added, "provides our first glimpse into (the) destabilization mechanism."

Nogales also found that Taxol inserts itself into the tubulin protein and prevents compaction of the alpha and beta subunits, so that no tension builds up. As a result, even if the microtubule stops growing, it remains intact, basically frozen in place, unable to peel apart, or depolymerize, and carry out its normal function.

"Taxol reverses the effects of GTP hydrolysis," she said.

Nogales and her team discovered these structural changes by pushing the limits of cryoelectron microscopy, a technique in which samples are frozen and probed with a high-powered electron beam. They have now achieved a resolution sufficient to see details smaller than 5 angstroms (one-tenth of a nanometer) across, which is about the size of five hydrogen atoms. While most information to date about the structure of tubulin inside the microtubule has come from the study of artificial, flat sheets of aligned strips of tubulin, Nogales was able to probe three-dimensional microtubules frozen into their natural state, with and without Taxol bound to tubulin. This comparison clearly showed the effect Taxol has on microtubule structure.

Other coauthors of the paper are former UC Berkeley biophysics graduate student Gregory M. Alushin, now of the National Heart Lung and Blood Institute in Bethesda, Md.; former LBNL postdoc Gabriel C. Lander, now of The Scripps Research Institute in La Jolla, Calif.; Elizabeth H. Kellogg of UC Berkeley; Rui Zhang of LBNL and David Baker of the University of Washington, Seattle.

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http://www.eurekalert.org/pub_releases/2014-05/uoh-oto052114.php

One-third of all brain aneurysms rupture: the size is not a significant risk factor

Size of an aneurysm has no great significance on the risk of rupture

The lifetime risk for rupture of a brain aneurysm depends heavily on the patient's overall load of risk factors. However, a recent study by researchers from the University of Helsinki and Helsinki University Central Hospital demonstrated that the size of an aneurysm has no great significance on the risk of rupture.

This is a unique study in that it monitored aneurysm patients over their entire lifetimes, whereas typical follow-up studies last only between one and five years in duration. The study is also exceptionally broad in scope; Dr. Seppo Juvela points out that the only other place where a study of similar scope has been conducted is Japan. "It is unlikely that another similar, non-selected lifetime follow-up study on aneurysm patients will ever be conducted again," he states.

Current care practices are based largely on the results of previous, shorter studies. Such studies have shown that the size of the aneurysm is the most significant factor predicting its risk for rupture. Consequently, small (<7mm) aneurysms have often

been left untreated, even though such aneurysms have also been known to rupture and cause brain haemorrhages.

The new study established that approximately one third of all aneurysms and up to one fourth of small aneurysms will rupture during a patient's lifetime. The risk of rupture is particularly high for female smokers with brain aneurysms of seven millimetres or more in diameter. What surprised the researchers most was that the size of an aneurysm had little impact on its risk for rupture, particularly for men, despite a previously presumed correlation. In addition, the risk of rupture among non-smoking men was exceptionally low.

"This is not to say that aneurysms in non-smoking men never rupture, but that the risk is much lower than we previously thought. This means treating every unruptured aneurysm may be unnecessary if one is discovered in a non-smoking man with low blood pressure," Juvela clarifies. But why have previous studies not reached these same results if they are so obvious?

"It is difficult to conduct reliable epidemiological research in brain aneurysms. The past 10 years have seen a distortion in the field due to a very limited group of researchers determining the direction for research. Now the situation is clearly changing, and clinically reasonable, population-based studies using non-selected data are on the rise again," states Docent Miikka Korja of the HUCS neurosurgery clinic.

Finland has a strong tradition of studying the prevalence, risk factors and care of brain aneurysms, and the Helsinki University Central Hospital is one of the world's leading units to provide treatment for brain aneurysms. Major studies in the field published by Finnish researchers include the world's most extensive twin study on the hereditability of subarachnoid haemorrhage, the largest follow-up study on subarachnoid haemorrhages among diabetics, the most extensive study on the life expectancy of subarachnoid haemorrhage survivors and a study on the risk factors for subarachnoid haemorrhages using the most extensive population data.

http://www.eurekalert.org/pub_releases/2014-05/uops-ctd052214.php

Clinical trials designed to block autophagy in multiple cancers show promise

Physician from Penn's Abramson Cancer Center leads clinical efforts to manipulate a new drug pathway in cancer patients

PHILADELPHIA— In the largest group of results to date, researchers from Penn Medicine's Abramson Cancer Center and other institutions have shown in clinical trials that the malaria drug hydroxychloroquine (HCQ) blocked autophagy in a host of aggressive cancers—glioblastoma, melanoma, lymphoma and myeloma, renal and colon cancers—and in some cases helped stabilize disease. Autophagy—an essential process cancer cells need to fuel their growth—is a key troublemaker spurring tumor growth. Block this pathway, many preclinical studies suggest, and anti-cancer agents such as chemotherapy and radiation therapy will be able to do their job better.

Results of six trials—five in humans (with over 200 patients) and one in dogs—are all reported in the May online issue of *Autophagy*, and will be presented at the Keystone Symposia on Autophagy in Austin, Texas, on Monday, May 26, by author Ravi K. Amaravadi, MD, assistant professor of Medicine in the division of Hematology/Oncology at the Perelman School of Medicine and co-leader of the Cancer Therapeutics Program at Penn Medicine's Abramson Cancer Center, who was the principal investigator on four of the six trials, which included a multi-disciplinary team of investigators at Penn Medicine and other institutions treating a wide range of cancers.

"There are currently over 40 clinical trials involving HCQ as a potential autophagy inhibitor worldwide, and the results of our trials are among the first to be published," said Amaravadi. "These studies provide promising evidence that autophagy blockade can be achieved, and that combining autophagy inhibitors with other cancer therapies in very sick patients can be accomplished safely in most cases. We wanted to present the data for all of these trials at one time, because when presented side by side, a more comprehensive and synergistic understanding of the potential of blocking this pathway emerges."

The phase I and phase I/II trials aimed to measure the safety of adding HCQ to either chemotherapy, radiation therapy or targeted therapies, its effectiveness at inhibiting autophagy, and the potential clinical benefit of HCQ combination therapies.

In melanoma, researchers observed prolonged stable disease in 20 percent of the patients on temozolomide. While in another trial, researchers observed stable disease in 75 percent of patients with metastatic melanoma on temsirolimus. In the dog clinical trial, all 30 dogs with non-Hodgkin's lymphoma treated with HCQ and the standard chemotherapy doxorubicin had clinical benefit, and nine had complete remission.

Autophagy is a relatively new target in cancer, infectious disease and neurodegenerative disorders, and while advances in the fundamental understanding of autophagy are increasing at a breakneck speed, translation of these advances into clinical trials and clinical benefit has been lagging. More recently, HCQ has shown promise in treating pancreatic cancer patients in ongoing clinical trials; however, its tolerability and effectiveness to stop autophagy in humans with other cancers has not been shown before.

The following is a brief summary of each of the six clinical trials, which can be found here.

Trial #1: A phase I/II trial of HCQ in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme

These data from a national trial with 92 glioblastoma patients established that autophagy inhibition is achievable with HCQ; however, toxicity prevented escalation to higher doses. Therefore, a definitive test of the role of autophagy inhibition in the adjuvant setting for glioma patients awaits the development of lower-toxicity compounds for optimal inhibition. No significant improvement in overall survival was observed.

Trial #2: Phase I trial of HCQ with dose-intense temozolomide in patients with advanced solid tumors and melanoma

A trial with 40 patients (73 percent with metastatic melanoma) showed that high-dose HCQ and the oral chemotherapy drug temozolomide is safe and tolerable, and is associated with autophagy inhibition. Prolonged stable disease and responses observed in about 20 percent of the patients suggests antitumor activity.

Trial #3: Combined autophagy and proteasome inhibition: A phase 1 trial of HCQ and bortezomib in patients with relapsed/refractory myeloma

A phase I trial with 25 patients combining bortezomib and HCQ for relapsed or refractory myeloma achieved autophagy inhibition and was tolerated. Of 22 patients evaluable for response, 3 (14 percent) had very good partial responses, 3 (14 percent) had minor responses, and 10 (45 percent) had a period of stable disease.

Trial #4: Combined mTOR and autophagy inhibition: Phase I trial of HCQ and temsirolimus in patients with advanced solid tumors and melanoma

This study of 27 patients indicates that temsirolimus, an mTOR inhibitor, and HCQ is safe and tolerable, blocks autophagy, and had significant antitumor activity; researchers observed stable disease in 75 percent of those patients with metastatic melanoma.

Trial #5: Combined autophagy and HDAC inhibition: A phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of HCQ in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumor.

A phase I clinical trial conducted by investigators at the University of Texas San Antonio, showed that the combination of HCQ and the chemotherapy drug vorinostat in 27 patients with advanced solid tumors, including renal cell carcinoma and colon cancer, was clinically safe and inhibited autophagy. What's more, one patient who had failed multiple prior treatments for renal cell carcinoma had a confirmed durable partial response and two patients with colorectal cancer had prolonged stable disease.

Trial #6: Phase I clinical trial and pharmacodynamic evaluation of combination HCQ and doxorubicin treatment in pet dogs treated for spontaneously occurring lymphoma

A phase I trial conducted by investigators at the Colorado State University Veterinary School in 30 dogs with non-Hodgkin's lymphoma with HCQ and the standard chemotherapy doxorubicin (DOX) showed a 100 percent clinical benefit rate. Nine of the dogs had complete remission. These results are encouraging given that reported response rates with DOX alone for treatment-naive lymphoma in dogs range from 60-85 percent. The tissue samples provided by the dogs provided valuable information about HCQ pharmacology and demonstrated that clinical trials in dogs can not only benefit pets, but can advance scientific knowledge.

"The promising safety results of these early trials set the stage for additional HCQ trials in different cancers, and trials involving new autophagy inhibitors that are being developed by pharmaceutical companies," said Amaravadi. "However, more work needs to be done before we can declare HCQ as a viable and cost-effective drug to help improve the efficacy of certain anti-cancer agents for the treatment of many cancers.

"If we can find the type of cancer patients for whom this approach works best, it could have a huge impact for global cancer care. In the meanwhile, cancer patients should only be treated with new HCQ combinations in the setting of a clinical trial."

Other institutions involved in the study include University of the Sciences, University of Texas San Antonio, Johns Hopkins University, Case Comprehensive Cancer Center, Dana-Farber/Harvard Cancer Center, Henry Ford Hospital , University of Alabama at Birmingham, University of California, San Francisco, Wake Forest University, University of Colorado – Aurora and Colorado State University-Fort Collins, CO.

http://www.bbc.com/news/magazine-27509559

Great miscalculations: The French railway error and 10 others

The discovery by the French state-owned railway company SNCF that 2,000 new trains are too wide for many station platforms is embarrassing, but far from the first time a small mis-measurement or miscalculation has had serious repercussions.

The French fiasco has been blamed by SNCF on the national rail operator RFF. But sometimes there is no-one else to share responsibility. Here are 10 examples where a little error has proved very **expensive, or even fatal.**

1. The Mars Climate Orbiter

Designed to orbit Mars as the first interplanetary weather satellite, the Mars Orbiter was lost in 1999 because the Nasa team used imperial units while a contractor used metric. The $125m probe came too close to Mars as it tried to manoeuvre into orbit,

and is thought to have been destroyed by the planet's atmosphere. An investigation said the "root cause" of the loss was the "failed translation of English units into metric units" in a piece of ground software.

2. The Vasa warship

In 1628, crowds in Sweden watched in horror as a new warship, Vasa, sank less than a mile into her maiden voyage, with the death of 30 people on board. Armed with 64 bronze cannons, it was considered by some to be the most powerful warship in the world. Experts who have studied it since it was raised in 1961 say it is asymmetrical, being thicker on the port side than the starboard side. One reason for this could be that the workmen were using different systems of measurement. Archaeologists have found four rulers used by the workmen who built the ship. Two were calibrated in Swedish feet, which had 12 inches, while the other two measured Amsterdam feet, which had 11 inches.

3. The "Gimli Glider"

In 1983, an Air Canada flight ran out of fuel above Gimli, Manitoba. Canada had switched to the metric system in 1970, and the plane is reported to have been Air Canada's first aircraft to use metric measurements. The plane's on-board fuel gauge was not working, so the crew used measuring "dripsticks" to check how much fuel the plane took on during refuelling. Things went wrong when they converted this measurement of volume into one of weight. They got the number right, but the unit wrong - mistaking pounds of fuel for kilograms. As a result the plane was carrying about half as much fuel as they thought. Luckily, the pilot was able to land the plane safely on the Gimli runway, giving the plane the nickname "Gimli Glider".

4. The Hubble Space Telescope

The Hubble telescope is famous for its beautiful space images, and is considered a great success for Nasa. However, it got off to a very rocky start. The first images sent back by the telescope were fuzzy because the telescope's main mirror was too flat. It wasn't out by much - only 2.2 microns, or about 1/50th the thickness of a human hair - but this was enough to put the project in jeopardy. One theory is that a speck of paint on a device used to test the mirror resulted in distorted measurements. Luckily, scientists managed to fix the problem in 1993, using an instrument called the Corrective Optics Space Telescope Axial Replacement (Costar). This cancelled out the error in the main mirror, by matching it in reverse.

5. Big Ben

The Big Ben bell at the Houses of Parliament in London cracked during testing in 1857 and was melted down to be recast. But the new bell, winched into position over three days in 1859, also quickly cracked. Disputes raged over who was at fault - there was even a libel case. One theory is that the massive hammer, at 6.5 hundredweight, was too heavy - at least for the particular alloy the bell was made from (seven parts tin to 22 of copper). The foundries which cast the bells had always argued this material was too brittle. The second bell was not replaced (it is still cracked), just rotated by an eighth of a turn. The hammer, however, was replaced by a lighter one.

6. Stonehenge model

In the 1984 mockumentary This is Spinal Tap, the members of a fictional rock group order a model of a Stonehenge megalith for their stage show - but the note written on a napkin mistakenly asks for a model 18 inches *(18")* tall, instead of 18 feet *(18')*. Curiously, and probably coincidentally, the British rock band Black Sabbath had experienced the opposite problem during its Born Again tour in 1983. Its replica of Stonehenge was so big, it got in the way of the band, and very few of the "stones" would fit on the stage. One version of the story says there was a mix-up between metres and feet.

7. The Laufenburg bridge

What is sea level? It varies from one place to another, and different countries use different benchmarks. "For example, Britain has measured height in relation to mean sea levels in Cornwall, while France measures height in relation to sea levels in Marseille," says Dr Philip Woodworth, of the National Oceanography Centre Liverpool. Germany, for its part, measures height in relation to the North Sea, while Switzerland, like France, opts for the Mediterranean Sea. This caused a problem in Laufenburg, a town that straddles Germany and Switzerland. As two halves of a new bridge grew closer to one another in 2003, it became clear that, instead of being at the same height "above sea level", one side was 54cm higher than the other. Builders knew that there was a 27cm difference between the two versions of sea level - but somehow it was doubled, rather than cancelled out. The German side reportedly had to be lowered before the bridge could be completed.

8. Scott's diet

The polar explorer Robert Falcon Scott made a fatal miscalculation about the amount of food his men would need on their 1910-1912 expedition to the South Pole. They were given rations of 4,500 calories per day, which is now known to be insufficient when hauling sledges, and especially at higher altitudes. According to Dr Mike Stroud, a polar veteran and expert in nutrition, the explorers were getting some 3,000 calories per day less than their bodies needed, and would have lost about 25kg of body weight before they reached their destination and started the return journey. Scott and his companions on the trek to the pole are now assumed to have died of starvation.

9. The Sochi biathlon track

The day before the opening of the Sochi Winter Olympics, it was discovered that the biathlon track - which should be a loop of 2.5km (1.6 miles) - was 40m (130ft)

short. Competitors in 7.5km events would have covered less than 7.4km, while those in 12.5km events would have done 12.3km. Some hasty repair work ensured the track was the right length for the first event three days later. Lengthening a biathlon track is clearly easier than lengthening a swimming pool. It's often been reported that 50m swimming pools at Crystal Palace in London and Leeds were made a few centimetres too short - sometimes, it's said, because the designers forgot about the thickness of the tiles. These stories, however, appear to be urban myths. A similar report about Portsmouth's Olympic pool in 2011 also turned out to be incorrect.

10. The Millennium Bridge

To mark the new millennium, London got a new footbridge in June 2000, linking the newly opened Tate Modern art gallery, on the south bank of the Thames, with the north bank near St Paul's cathedral. But people noticed that the 350m-long structure wobbled alarmingly as they walked across. One of the difficulties of designing a footbridge is the "synchronised footfall" effect - as the bridge begins to bounce or sway people adjust their footsteps to the rhythm of the bridge's movements, inadvertently magnifying them. In this case, the designers took account of the up-and-down synchronised footfall, but not the side-to-side effect. The following year, work began to install dampers, like car shock absorbers, to reduce the rocking. It was reopened in February 2002.

http://bit.ly/1nIc6Io

The Science Of Misheard Song Lyrics

There is an actual official term for when you hear "excuse me while I kiss the sky" in Jimi Hendrix's "Purple Haze" as "excuse me while I kiss this guy."

Esther Inglis-Arkell

Your meaningful misheard lyrics are called "mondegreens," and their study can have real psychological significance.

We've all had those awkward moments. A group of friends is singing in a car, and suddenly, someone says the wrong word. And everyone looks at each other, wondering how that person heard the wrong song lyrics, or whether they themselves are wrong. These little misunderstandings are common, but most people don't know that there is an official title for them. It came from a popular essay by writer Sylvia Wright, where she recalled when her mother read a certain book of poems to her. One of the verses was as follows:

Ye Highlands and ye Lowlands,
Oh, where hae ye been?
They hae slain the Earl o' Moray,
And Lady Mondegreen.

Readers will be glad to know that Lady Mondegreen was spared the slaughter, but only because she never existed. The actual last line of the verse was, "And laid him on the green." Wright christened these misheard lyrics, which often make the poem or song better for the listener, "mondegreens." The title caught on.

Mondegreens and What They Mean

Sometimes the mondegreens make more sense than the original lyrics, but such a happy coincidence is a rare event. What's interesting is everyone has an explanation of their particular mondegreen.

I heard "I can feel it coming in the air tonight," as "I can hear it coming in the yellow night," well into my college years, and thought Phil Collins was just being poetic. A friend of mine claims both her parents, independently, heard Creedence Clearwater Revival's "There's a bad moon on the rise," as "There's a bathroom on the right." She had to be born, grow up, listen to the song herself, and correct them before they even considered that they were wrong. When she asked them how they thought the lyrics were directions to the bathroom, her father answered, "I just figured they were stoned." Which is as good an explanation as any.

Mondegreens are often measures of experience. (This is why we all kept an eye on my brother when he heard the doo-wop song "Who Wrote the Book of Love" as "Who Let the Great Horse Die." It was probably an innocent mistake but we didn't want an amateur production of Equus on our hands.) This is why the signature phrases of most songs are misinterpreted. The lyrics that defy cliche and break new ground are most likely to get misunderstood. "Excuse me, while I kiss this guy" might have still been outré in the 1960s when "Purple Haze" was written, but it was still more familiar than kissing the sky. We cobble together a semi-plausible lyric because we lack the experience to understand the real one. The people who are most likely to do this are the ones most lacking in experience.

Children, Language Learners, and Mondegreens

Kids learn by ear, and they know that they're still learning words, so they are particularly vulnerable to mondegreens. One class of children, when asked to copy out the lyrics to "The Star-Spangled Banner," wrote, "Oh say can you see, by the donzerly light." Children group words together, the way they hear them, in a stream of continuous syllables. They assume the meaning of "donzerly" will come later, when they hear a few more examples of the word. We enunciate for small babies, but as children grow, they are expected to pick up individual words, many of which they've never been exposed to, in a stream of noise. Language learners also have difficulty distinguishing one word from another, which can run them into real trouble in business or medical settings.

A surprising amount of tests for which words tend to throw people off involve exactly what we do in cars — listening to song lyrics. Children and English learners

transcribe the words, and psychologists try to figure out what characteristics of the speaker, or the words, make people mentally squish words together.

Many researchers have found that mondegreens tend not to travel alone. Once people lose understanding of a sentence, they lose context as well, causing them to "hear" words that only resemble the actual words being uttered. People, especially adult English learners, are desperately trying to regain the thread of meaning, and make order out of a chaos of sounds. Eventually they trick themselves into hearing something that the recognize, even if it doesn't make sense. What most people need, scientists find, is familiar points where they can get their bearings, and enter back into the thread of the conversation. If they can't get regular familiar points to orient themselves in a stream of sound, mondegreens will take over and give them fake points of familiarity.

[Via Mondegreens: Of Cross-Eyed Bears and Falling Rocks, The Raising of Baby Mondegreen, Helping Listeners Avoid Mondegreens, Music and Mondegreens]

http://wrd.cm/1h2lTdU

Absurd Creature of the Week: The 2,500-Pound Snake That Devoured Gigantic Crocodiles

By far the biggest snake that ever lived

By Matt Simon

Long ago, legend has it, the god Thor and the giant Hymir rowed to sea in search of Jörmungandr, a snake so huge it circled the Earth. Thor dropped a line baited with an ox head, which Jörmungandr nommed on, and with his bare hands reeled the beast in. Once the serpent was at the edge of the boat, though, Hymir got all nervous and cut the line.

But what I do know is that 60 million years ago, in the swampy waters of what is now Colombia, there lurked a serpent of similar hyperbole: titanoboa, by far the biggest snake that ever lived. At nearly 50 feet long and weighing in at 2,500 pounds, it was 10 times as heavy as the average green anaconda, a giant that now rules titanoboa's stomping grounds… or slithering grounds, I guess you'd say.

Titanoboa was so big, it pushed the boundaries of being able to exist on land and remain in accordance with the laws of physics. You, me, every cat and antelope and towering sauropod, we've all evolved under the constraints of gravity. Evolution got a bit carried away and produced the 100-foot blue whale, the biggest critter ever, only because gravity doesn't affect giants as much in the sea.

Scientists reckon titanoboa must have also exploited this kind of simulated weightlessness. It was so outsized that "almost certainly it would have spent a large part of its time in water," said David Polly, a vertebrate paleontologist at Indiana University. "And we know that both from the geology where it's preserved but also by inference of how big it was. It just wouldn't have been able to get around on land very well."

Snakes, you see, are deceptively good swimmers, kinda like sloths. (Seriously, have you ever seen a sloth swim? They're way faster in water than on land.) Titanoboa wouldn't have had quite the agility of, say, a sea snake, but it didn't need to dart around anyway.

Titanoboa sunning on a beach, totally unaware of the social-media catastrophe that would swirl around it in 60 million years. **Illustration: Jason Bourque, Florida Museum of Natural History**

This was likely an ambush hunter, a constrictor of enormous proportions that relied not on venom, but on its incredible strength to squeeze the life out of its prey. Anacondas do the same, and indeed scientists believe titanoboa behaved much like them.

Lying in wait on shallow river and swamp bottoms, anacondas can hold their breath for up to 45 minutes, or simply rest with their noses poked out of the water. They dig themselves into the sediment–rotting leaves and such–and wait for a hapless capybara to amble through. Its strike is blindingly fast, its constriction unmerciful. Not only can the prey not breathe, its blood can't even circulate.

Now scale that up 10 times. Large mammals such as the capybara (the world's biggest rodent) hadn't yet appeared on Earth, so instead titanoboa was hunting lungfish 7 feet long, plus huge turtles and crocodiles. The serpent, it seems, wasn't the only giant of its time. And there's a very good reason for that.

As you probably learned from the poor classroom garter snake you and your friends tortured as kids, reptiles need an external source of heat to power their metabolism and slither away from your tiny grabby hands. They'll grow continuously their whole lives–reaching a plateau eventually and slowing down, sure, but they're always expanding. And, among other things, what puts a maximum size cap on snakes is their ambient temperature.

Unfortunately for titanoboa's prey, "the climate in the Paleocene when this animal lived was much warmer than it is today," said Polly. "And that would have allowed for bigger reptiles, and indeed not only is there titanoboa, but even in the same site there are crocodiles and turtles that are a lot larger than any living today."

Imagine 5 feet in length for the turtles and 20 feet for the crocs. Still, they were no match for titanoboa, an apex predator among apex predators (though the larger saucer-shaped turtles, in a sort of final statement, would have left the snakes with fairly comical bulges). And doubly unfortunate for those lower on the food chain was that across the world around this time, there were any number of snakes super-sized by warming climates, the second largest after titanoboa being gigantophis at 33 feet long.

Now, typically for endothermic–so-called "warm-blooded"–critters, the opposite trend is true. Larger body sizes, such as that of the polar bear, are better suited for frigid environments because the bigger you are, the lower your surface-area-to-volume ratio, and thus the better you retain heat. This is known as Bergmann's rule. Mammals have sweat glands to cool themselves if they overheat, but snakes have no such luxury. And a humongous snake smack in the middle of the tropics could find itself very toasty indeed.

So how did it keep from cooking? Polly reckons that its aquatic lifestyle would have done well to regulate its body temperatures. Cool too much, and titanoboa could emerge to sunbathe. Thus these oversized reptiles could manage their temperature in the unrelenting tropical heat like finicky old folks in Florida shuffling in and out of pools.

Why, and even when, titanoboa went extinct remains a mystery, but we can thank what fossils we do have on the environment they occupied. Perishing on river bottoms, titanoboas found protection from scavengers and the ravages of the elements. And such swampy waters naturally produce excellent fossils, not to mention the coal that for better or worse still powers our world.

Titanoboa fossils are "recovered from what is one of the largest open coal mines in the world, the Cerrejón coal mine," said Polly. "And coal is made from the plant remains that essentially fall into the water where they don't decay as rapidly, and they get buried in the sediments that are coming into the water," by way of something like a flood.

Over geologic time, these layers turn to different kinds of rock: Paleontologists find titanoboa fossils in the rocks built from the sediments, specifically clay, while the miners toiling around them are obviously more interested in the pure plant-derived coal.

Thus science and industry, so often at odds, can finally agree to appreciate a Colombian coal deposit. That is, until our wanton burning of fossil fuels heats our planet to the temperatures required to nurture the next titanoboa in South America. Any humans left by that time will, I hope, appreciate the irony.

http://www.eurekalert.org/pub_releases/2014-05/nuos-bmf052314.php

Breakthrough method for making Janus or patchy capsules

Tiny capsules with different substances on their surface could be useful in medicine and materials technology

Hollow capsules that have a selectively permeable shell are promising candidates as tiny containers for molecules, particles or bubbles, and are becoming increasingly important in a wide variety of applications. But making these kinds of capsules with more than one kind of substance on their shells has been challenging – until now.

In a article in the latest edition of Nature Communications, NTNU researcher Jon Otto Fossum and Paul Dommersnes from the University of Paris, Diderot, were part of a team that showed that both Janus and more advanced patchy capsules can be assembled by combining electro-coalescence and electro-hydrodynamic flow in leaky dielectric emulsion drops. This technique can be used with any type of insulating or weakly conductive particles.

Their work is the realization of one possible direction foreseen by the same researchers in a publication in Nature Communications in 2013.

Hollow capsules with two or more substances on their surface are able to organize themselves in specific ways, which means they could be used to grow human skin or other body tissues, or to make porous tissues and composites. They can also be used to transport a variety of substances and release them in specific environments.

Janus capsules, named for the two-faced Roman god, have just two different substances in their shells. They are a sub-group of patchy capsules, which can have more than two different substances in their shells. The researchers were able to make both Janus capsules, with two different substances, and patchy capsules, which had stripes or flecks on them.

Janus and patchy capsules are distinct from Janus and patchy particles, which are solid. These capsules combine the characteristics of Janus or patchy particles, and those of capsules such as colloidosomes.

The different characteristics on the shells of the capsules make them attractive to each other in different ways, depending on the composition of the capsule shells, which means they can create scaffolds suitable for biomedical applications, for assembling electric circuits or optical structures such as photonic crystals, and as vehicles for liquid or molecular transport. The researchers foresee that their route for designing patchy capsules will facilitate the foundation for many advanced applications, for example, by using microfluidic methods.

The article "Electroformation of Janus and patchy capsules" is in Nature Communications 5:3945 (2014), DOI: 10.1038/ncomms4945.

It is open access and can be viewed at:

http://www.nature.com/ncomms/2014/140523/ncomms4945/full/ncomms4945.html

http://bit.ly/1ih5a19

New malaria vaccine traps the disease inside the blood cells it infects

New approach intended to imprison malaria-causing parasites inside the red blood cells

By Reuters: Reporting by Will Dunham; Editing by James Dalgleish

WASHINGTON - Scientists seeking a vaccine against malaria, which kills a child every minute in Africa, have developed a promising new approach intended to imprison the disease-causing parasites inside the red blood cells they infect.

The researchers said on Thursday an experimental vaccine based on this idea protected mice in five trials and will be tested on lab monkeys beginning in the next four to six weeks.

Dr. Jonathan Kurtis, director of Rhode Island Hospital's Center for International Health Research, said if the monkey trials go well, a so-called Phase I clinical trial testing the vaccine in a small group of people could begin within a year and a half.

Using blood samples and epidemiological data collected from hundreds of children in Tanzania, where malaria is endemic, by Drs. Patrick Duffy and Michal Fried of the U.S. National Institutes of Health, the researchers pinpointed a protein, dubbed PfSEA-1, that the parasites need in order to escape from inside red blood cells they infect as they cause malaria.

The researchers then found that antibodies sent by the body's immune system to take action against this protein managed to trap the parasites inside the red blood cells, blocking the progression of the disease.

Scientists have struggled for years to create an effective vaccine against malaria, a mosquito-borne disease that the U.N. World Health Organization estimates kills 627,000 people a year, mostly children in sub-Saharan Africa. "It's profoundly important to develop an effective malaria vaccine," said Dr. Anthony Fauci, director of the NIH's National Institute of Allergy and Infectious Diseases, calling the study "a novel and different type of an approach toward a vaccine."

"Since the malaria parasite has such a complex replication cycle, there are multiple points in that replication cycle that are vulnerable to interference by an antibody or some response that can be induced by a vaccine," Fauci told Reuters.

'A Burning House'

Microscopic malaria parasites are carried in the saliva of female mosquitoes and enter a person's bloodstream through the insect's bite. The parasites pass through the liver and infect red blood cells. They replicate wildly in these cells and cause them to rupture, flooding the body with more and more parasites.

Two existing approaches to vaccine development have sought to block the parasites from entering the liver or red blood cells. The new approach instead tries to bottle them up inside the red blood cells – or, as Kurtis put it, "trap them inside a burning house."

If the parasites remain trapped, they can be harmlessly gobbled up in the spleen by immune system cells called macrophages, Kurtis said.

The researchers developed a vaccine that targeted PfSEA-1 and tried it on mice. In five experiments, vaccinated mice that were exposed to malaria had parasite levels four times lower than unvaccinated mice and survived twice as long afterward.

The researchers then looked at blood samples from some of the Tanzanian children. Roughly one in 20 had naturally occurring levels of the antibodies that target PfSEA-1, and among these children there were no cases of severe malaria.

The researchers also examined blood samples from 138 boys and men from a malaria-endemic area of Kenya. Those with detectable levels of naturally occurring antibodies to PfSEA-1 had 50 percent lower parasite levels than those who did not.

Kurtis expressed hope about the prospects of a vaccine targeting this protein, but said the best future vaccine likely would combine this approach with others to attack the parasite on several fronts. He noted that there is currently no licensed vaccine for human parasitic infection.

The study was published in the journal Science.

http://scitechdaily.com/new-data-nasa-conflicts-black-hole-doughnut-theory/

New Data from NASA Conflicts with Black Hole 'Doughnut' Theory

New Study Pokes Holes in Black Hole Doughnut Theory

New data from NASA's Wide-field Infrared Survey Explorer reveals a new feature about active black holes, leaving astronomers to reexamining a decades-old theory about the varying appearances of these interstellar objects.

A survey of more than 170,000 supermassive black holes, using NASA's Wide-field Infrared Survey Explorer (WISE), has astronomers reexamining a decades-old theory about the varying appearances of these interstellar objects.

The unified theory of active, supermassive black holes, first developed in the late 1970s, was created to explain why black holes, though similar in nature, can look completely different. Some appear to be shrouded in dust, while others are exposed and easy to see.

The unified model answers this question by proposing that every black hole is surrounded by a dusty, doughnut-shaped structure called a torus. Depending on how these "doughnuts" are oriented in space, the black holes will take on various appearances. For example, if the doughnut is positioned so that we see it edge-on,

the black hole is hidden from view. If the doughnut is observed from above or below, face-on, the black hole is clearly visible.

However, the new WISE results do not corroborate this theory. The researchers found evidence that something other than a doughnut structure may, in some circumstances, determine whether a black hole is visible or hidden. The team has not yet determined what this may be, but the results suggest the unified, or doughnut, model does not have all the answers.

"Our finding revealed a new feature about active black holes we never knew before, yet the details remain a mystery," said Lin Yan of NASA's Infrared Processing and Analysis Center (IPAC), based at the California Institute of Technology in Pasadena. "We hope our work will inspire future studies to better understand these fascinating objects."

Yan is the second author of the research accepted for publication in the Astrophysical Journal. The lead author is post-doctoral researcher, Emilio Donoso, who worked with Yan at IPAC and has since moved to the Instituto de Ciencias Astronómicas, de la Tierra y del Espacio in Argentina. The research also was co-authored by Daniel Stern at NASA's Jet Propulsion Laboratory (JPL) in Pasadena, and Roberto Assef of Universidad Diego Portales in Chile and formerly of JPL.

Every galaxy has a massive black hole at its heart. The new study focuses on the "feeding" ones, called active, supermassive black holes, or active galactic nuclei. These black holes gorge on surrounding gas material that fuels their growth.

With the aid of computers, scientists were able to pick out more than 170,000 active supermassive black holes from the WISE data. They then measured the clustering of the galaxies containing both hidden and exposed black holes — the degree to which the objects clump together across the sky.

If the unified model was true, and the hidden black holes are simply blocked from view by doughnuts in the edge-on configuration, then researchers would expect them to cluster in the same way as the exposed ones. According to theory, since the doughnut structures would take on random orientations, the black holes should also be distributed randomly. It is like tossing a bunch of glazed doughnuts in the air — roughly the same percentage of doughnuts always will be positioned in the edge-on and face-on positions, regardless of whether they are tightly clumped or spread far apart.

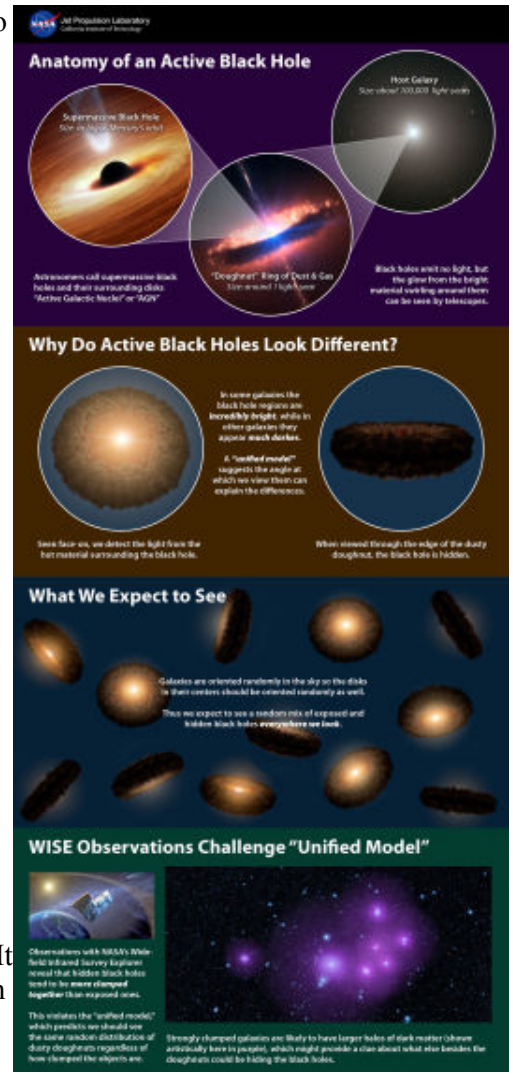
But WISE found something totally unexpected. The results showed the galaxies with hidden black holes are more clumped together than those of the exposed black holes. If these findings are confirmed, scientists will have to adjust the unified model and come up with new ways to explain why some black holes appear hidden.

"The main purpose of unification was to put a zoo of different kinds of active nuclei into a single umbrella," said Donoso. Now, that has become increasingly complex to do as we dig deeper into the WISE data."

Another way to understand the WISE results involves dark matter. Dark matter is an invisible substance that dominates matter in the universe, outweighing the regular matter that makes up people, planets and stars. Every galaxy sits in the center of a dark matter halo. Bigger halos have more gravity and, therefore, pull other galaxies toward them.

Because WISE found that the obscured black holes are more clustered than the others, the researchers know those hidden black holes reside in galaxies with larger dark matter halos. Though the halos themselves would not be responsible for hiding the black holes, they could be a clue about what is occurring.

"The unified theory was proposed to explain the complexity of what astronomers were seeing," said Stern. "It seems that simple model may have been too simple. As Einstein said, models should be made 'as simple as possible, but not simpler.'"



This infographic explains a popular theory of active supermassive black holes, referred to as the unified model - and how new data from NASA's Wide-field Infrared Survey Explorer, or WISE, is at conflict with the model. **Image Credit: NASA/JPL-Caltech/NOAO/AURA/NSF/ESO**

Scientists still are actively combing public data from WISE, put into hibernation in 2011 after scanning Earth's entire sky twice. WISE was reactivated in 2013,

renamed NEOWISE, and given a new mission to identify potentially hazardous near-Earth objects.

Publication: Accepted for publication in Astrophysical Journal

PDF Copy of the Study: The Angular Clustering of WISE-Selected AGN: Different Haloes for Obscured and Unobscured AGN

http://www.medscape.com/viewarticle/825434?src=rss#1

Why You Should Consider This New Menopause Drug

Hello. This is Dr. JoAnn Manson, Professor of Medicine at the Harvard Medical School at Brigham and Women's Hospital.

JoAnn E. Manson, MD, DrPH

Today I want to talk about a new combination medication: bazedoxifene, a selective estrogen receptor modulator, combined with conjugated estrogens, marketed as Duavee™. Should we be adding this medicine to our treatment arsenal for menopause management?

As you know, this medication was approved by the US Food and Drug Administration last year for the treatment of vasomotor symptoms and the prevention of osteoporosis in postmenopausal women with an intact uterus. But only in the past several months has a critical mass of research and literature[1-4] been published -- in the journals Menopause and Clinical Endocrinology and Metabolism, and other journals -- that really helps to inform clinical decision-making about the use of this medication. I want to mention that I have no financial conflicts of interest, and I have received no form of funding related to this product.

Bazedoxifene is an estrogen agonist and antagonist. It has agonist effects in the bone and antagonist effects in the endometrium. Postmenopausal women who have an intact uterus and take estrogen with progestin have a higher risk for irregular vaginal bleeding, increased breast density, and breast pain. The Women's Health Initiative suggested that these women also had increased risk for breast cancer, venous thromboembolism, stroke, and heart disease. Conjugated estrogen alone was not linked to an increased risk for breast cancer or heart disease in the Women's Health Initiative, although it was associated with an increased risk for stroke and venous thrombosis.

Findings From Bazedoxifene/Conjugated Estrogen Trials

To date, the randomized trials of bazedoxifene 20 mg combined with conjugated estrogen 0.45 or 0.625 mg per day have shown substantial reductions in the frequency and severity of hot flashes, night sweats, and vasomotor symptoms. These trials have also shown increased bone mineral density in the lumbar spine and hip, compared with placebo. A previous randomized trial[5] of bazedoxifene alone at a dose of 20 mg resulted in a significantly reduced risk of vertebral fracture. Overall, these trials have suggested no increase in breast density, breast pain, or any endometrial problems; the endometrial changes seen with use of this combination medication were similar to those seen with placebo. There also has not been any clear signal of an elevated risk for venous thromboembolism, stroke, or heart disease, although these trials have not been large enough or of long-enough duration to rule out an adverse cardiovascular effect with long-term use, and in particular to rule out an increased risk for venous thromboembolism or stroke.

Overall, the trials have indicated reductions in vasomotor symptoms and improvements in bone mineral density compared with placebo, and it does appear that this medication would be an appropriate option for selected patients, especially women who are at higher risk of developing osteoporosis and those who want to avoid the use of progestin.

Thank you very much for your attention. This is JoAnn Manson.

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http://scitechdaily.com/astronomers-solve-mystery-gamma-rays-originate/

Astronomers Solve the Mystery of Where Gamma Rays Originate

Astronomers Confirm Link between Gamma Bursts and Their Counterparts

An international team of astronomers has for the first time confirmed a link between the gamma bursts and their counterparts in several radio frequencies, solving the mystery of the origin of the outbreaks.

Blazars are among the largest and most energetic objects in the universe. Jets of matter (“jets”) shoot from the cores of these active galaxies shoot, which are accompanied by huge bursts of gamma rays. An international team led by Lars Fuhrmann from Bonn’s Max Planck Institute for Radio Astronomy has now for the first time confirmed a link between the gamma bursts and their counterparts in several radio frequencies. Furthermore, the researchers solved the mystery of the

origin of the outbreaks: These come from the immediate vicinity of the supermassive black holes at the center of blazars.

Special types of distant active galaxies and their innermost central regions show extreme physical processes. In the vicinity of a spinning supermassive black hole (billions of times heavier than our Sun) an enormous amount of energy is released, often in the most energetic form of light: high energy gamma-ray photons at mega- or even gigaelectronvolt (MeV/GeV) energies. This energy output is produced by feeding the black hole from surrounding stars, gas and dust. Matter is spiraling in onto the black hole and strong magnetic fields channel some of the infalling gas into two powerful, well collimated "jets" of plasma accelerating away from the center with velocities approaching the speed of light. Many of the connected physical processes are not understood in detail so far, for example the production of high-energy gamma-ray photons and their place of origin inside the jet, or the origin of strong outbursts of emission across the whole electromagnetic spectrum. New instruments and observing programs covering a large fraction of the whole energy spectrum nearly simultaneously allow new insights into the extreme physics of these objects to be obtained.

Using a combination of three of the world's most advanced single-dish radio observatories, namely the Effelsberg 100-m, IRAM 30-m and APEX 12-m telescopes covering quasi-simultaneously 11 radio frequency bands (the so-called Fermi-GST AGN Multi-frequency Monitoring Alliance, F-GAMMA program), the team of scientists was able to monitor the frequently occurring radio outbursts of about 60 powerful active galaxies over many years. "Since the era of the EGRET instrument on the Compton Gamma-ray Observatory in the 1990s, it has been discussed whether outbursts of radio emission are physically connected to similar events occurring at gamma rays" says Anton Zensus, Director at the Max Planck Institute for Radio Astronomy (MPIfR) and Fermi Affiliated Scientist. "Now with the combination of F-GAMMA radio and Fermi gamma-ray long-term data, and thanks to special analysis techniques, we finally know it!"

In addition to radio data within the F-GAMMA program, the research team used gamma-ray observations of NASA's Fermi Gamma-ray Space Telescope (launched in 2008), and a new statistical method to add up many radio and gamma-ray events. "It was illuminating to see the statistical noise going down and the average correlation popping up" explains Stefan Larsson, from Stockholm University. "This finally demonstrates that a significant connection exists, even when using different radio frequencies" he continues. The study furthermore shows that the radio outbursts arrived at the telescopes later in time than their gamma-ray counterparts, with mean delays between 6 and 7 days. "For the first time we see that the radio delays become smoothly smaller towards higher radio frequencies", adds Emmanouil Angelakis from MPIfR. "This tells us that the gamma-ray photons are coming from the innermost radio emitting jet regions."

Using the measured time delays the team was finally able to estimate distances of a few ten light years or less between the radio and gamma-ray outburst regions. "Based on our delay measurements we could estimate for one of the brightest gamma-ray emitting active galaxies in the sky, 3C 454.3, how far away from the supermassive black hole most of the gamma-ray photons must have been produced. We are talking about only a few light year distances – very close to the footpoint of the jet and the black hole itself!" proudly reports Lars Fuhrmann from MPIfR, the lead author of the paper. "This has serious implications for the physical processes producing the gamma-ray photons!" he adds. In the meantime the team is continuing to use the "Joint Eye" on the universe to collect more data and more events for detailed follow-up studies.

Publication: L. Fuhrmann, et al., "Detection of significant cm to sub-mm band radio and γ-ray correlated variability in Fermi bright blazars," MNRAS (July 1, 2014) Vol. 441 1899-1909; doi:10.1093/mnras/stu540

http://nyti.ms/1h2sJA8

When Cannabis Goes Corporate

New federal regulations in Canada make way for the large-scale legal production of marijuana.

By IAN AUSTENMAY 24, 2014

Hershey stopped producing chocolate in Smiths Falls, Ontario, six years ago. The work went to Mexico, but the factory remains, along with reminders of the glory days: A sign that once directed school buses delivering children for tours. A fading, theme-park-style entrance that marks what used to be the big attraction - a "Chocolate Shoppe" that sold about $4 million of broken candy and bulk bars a year.

The once ever-present sweet smell of chocolate is gone, too. In the high-ceilinged warehouse, where stacks of Hershey's bars and Reese's Peanut Butter Cups once awaited shipment, the nose now picks up a different odor: the woody, herbal aroma of 50,000 marijuana plants.

Clinical, climate-controlled rooms with artificial sunlight house rows upon rows of plants at various stages of growth. In the "mother room," horticulturalists use cuttings to start new plants. The "flowering rooms" are flooded with intense light 12 hours a day to nurture nearly grown plants in strains with vaguely aristocratic names like Argyle, Houndstooth and Twilling.

The new owner of this factory, at 1 Hershey Drive, is Tweed Marijuana. It is one of about 20 companies officially licensed to grow medical marijuana in Canada.

A court ordered the government to make marijuana available for medicinal purposes in 2000, but the first system for doing so created havoc. The government sold directly to approved consumers, but individuals were also permitted to grow for their own purposes or to turn over their growing to small operations. The free-for-all approach prompted a flood of complaints from police and local governments. So the Canadian government decided to create an extensive, heavily regulated system for growing and selling marijuana. The new rules allow users with prescriptions to buy only from one of the approved, large-scale, profit-seeking producers like Tweed, a move intended to shut down the thousands of informal growing operations scattered across the country.

The requirements, which went into effect in April, are giving rise to what many are betting will be a lucrative new industry of legitimate producers. The government, which will collect taxes on the sales, estimates that the business could generate more than 3.1 billion Canadian dollars a year in sales within the next decade.

"It's just so rare that you have an industry that's growing but which has a huge established market," said Chuck Rifici, Tweed's chief executive. "A year ago, if you asked me if I'd be working while looking at thousands of pot plants, I would never have thought that would be the case." Before deciding to focus on the marijuana business, he worked as a financial consultant to technology start-up companies in Ottawa, less than an hour's drive to the north.

Canada is not unique in transforming once-forbidden cannabis into a legal, or at least tolerated, proposition. The Netherlands has long allowed personal possession and cultivation of small quantities while allowing commercial sales through licensed cafes. Spain permits growing for personal use. Portugal has decriminalized possession of small quantities of all drugs.

In the United States, 20 states and the District of Columbia have legalized medical marijuana; both Washington State and Colorado have legalized recreational use with conditions.

But marijuana remains illegal under federal law, creating uncertainty; the federal government, for example, recently banned state-legal marijuana growers from using federal water on their crops.

Canada's across-the-board law, by contrast, provides a cohesive set of regulations, laying the groundwork for a group of companies to set up operations.

"That was really important for us as investors," said Brendan Kennedy, chief executive of Privateer Holdings, a marijuana private equity fund based in Seattle that started Tilray, one of Canada's new legal growers. "People talk about the Colorado model; people talk about the Washington model. I think someday they'll talk about the Canada model. By creating a tightly regulated federal system, by creating a federal license, by making it difficult to navigate in and capital-intensive, Canada has attracted a different kind of player into this industry."

'Why Not Smiths Falls?'

For most of its recent history, Smiths Falls (population 9,000) was defined by two things: the 19th-century canal that passes through its center and the chocolate-scented air. The Hershey plant, which had about 800 employees at its peak, was a vital part of the economy. Until a recent repainting, the town's water tower featured the Hershey's logo and declared Smiths Falls "the Chocolate Capital of Ontario."

"It was a huge tourist attraction for the town," Dennis W. Staples, the town's mayor, said of the Hershey's factory, which lured about 400,000 visitors a year. "They were without a doubt an excellent corporate citizen." The company sponsored sports teams and hockey tournaments and helped underwrite a "chocolate and railway" festival each summer.

The relationship seemed so fixed — the factory had been there for more than 40 years — that Mr. Staples was a bit puzzled in February 2007 when reporters called asking for comment on Hershey's plan to leave town. No one had told Mr. Staples. "Probably not the best way to communicate to the mayor," he said.

Hershey shut down its conveyor belts in 2008. But that was just the beginning of the bad news for Smiths Falls. A year later, the province of Ontario closed a nearby home for up to 2,650 developmentally disabled adults. Stanley Tools, an industrial company, left, as did two other American manufacturers. And a portion of the Canadian Pacific Railway's old transcontinental line, for which Smiths Falls was a regional hub, was ripped up. In all, about 1,700 jobs vanished, according to Mr. Staples.

At first, Hershey promised to help the town find a new business to take over the plant. A flavored-water company expressed interest but couldn't get the money together. In 2012, Hershey sold the plant to a holding company controlled by the Omnicom Group, the ad-agency giant. The new owner inquired about demolition permits last summer.

Around the same time, Mr. Rifici, who lives in Ottawa, showed up in Smiths Falls. Mr. Staples and the town council were supportive. They believed that Tweed would help stem, even if just a little, the outflow of jobs and investment.

"If it's going to happen somewhere in Canada, why not Smiths Falls?" Mr. Staples said. "It's an opportunity to be part of an industry that's sanctioned by the federal government," he said. "It's going to create 100 jobs."

The mayor also had a personal reason. When his younger brother was dying from colon cancer 11 years ago, marijuana was the only way he found relief from his pain.

Despite the warm welcome, Tweed has had to overcome the stigma of a once-illicit business. Mr. Rifici said the factory owner wouldn't lease the plant to a start-up focused on marijuana. So Mr. Rifici and his business partner Bruce Linton had to form a small investment pool to buy the plant for an undisclosed amount.

Continue reading the main story

Even once in the building, Mr. Rifici said it was impossible to get a bank loan to buy equipment. Initially, Tweed raised money from private investors. More recently, the company has tapped the public markets for 15 million Canadian dollars by issuing stock.

Other licensed marijuana-growing operations have faced similar impediments. When Privateer decided to start Tilray, for example, Mr. Kennedy crisscrossed Canada to find the right spot. It was apparent, he said, that Privateer would hit resistance in many areas. Illegal growing operations had attracted widespread negative publicity for destroying rental houses with mold and creating fire hazards with their lighting systems.

In Nanaimo, British Columbia, Mr. Kennedy found economic development officials who eagerly courted Tilray. The city was looking for new businesses to offset a gradual decline of the forestry and fishing industries, the region's historical economic base. The officials introduced local zoning bylaws that made it easier for the medical marijuana industry to operate.

Tilray has since bought a building for $3.5 million and spent $17 million to renovate it. The company employs 65 people, with plans to increase that number to 100. "One hundred new jobs in a community of less than 100,000, that's a big deal," Mr. Kennedy said.

Still, he said it took a while to find a bank that would deal with a marijuana grower. The Royal Bank of Canada eventually agreed to take Tilray's account and to process its credit card transactions.

Nor has Tweed won over everyone in Smiths Falls. Like many small, blue-collar towns in rural North America, it has an illegal-drug problem, mainly crack cocaine and marijuana.

Darlene Kantor, 50, works as a building manager, and she says she is thrilled that Tweed came to town with its jobs and millions of dollars of investment. "But my main concern is: Is it going to make the illegal drugs more rampant?" she said.

Some are more skeptical about whether Tweed will be able to provide many jobs. "They were talking about creating jobs and such, and it's not going to, it's not going to do anything," said Andrew Brinkworth, 18, outside the downtown Tim Hortons. "A lot of people here have criminal records, and they're not going to be able to get a job at the plant if they have a record."

A 300-Page Application

Dressed in a casual shirt and slacks, Mr. Rifici, 39, is built from an entrepreneurial mold. His fast speech and seemingly inexhaustible enthusiasm appear to be byproducts of pitching start-up ideas to investors, or anyone who will listen, for two decades.

His early interest in the Internet came from playing simple, text-based games. "Slaying virtual dragons with someone from Australia from my computer in my parents' basement in 1991-92 was eye-opening to how the Internet would fundamentally alter how we lived," he said. "So I had to get involved in some way."

In 1995, during his third year of computer engineering studies at the University of Ottawa, he decided to start an Internet service provider. He sold the business in 2003 for 1.1 million Canadian dollars ($1 million) to a larger competitor, Cybersurf, where he became chief financial officer. Over the next two decades, he helped start a dozen tech companies.

His interest in politics indirectly inspired his marijuana business. Mr. Rifici, who volunteers as chief financial officer of the Liberal Party of Canada, one of the three main national parties, closely tracked the evolution of marijuana laws.

In October 2012, Health Canada, the federal agency responsible for drug controls, published a long, technical list of proposed reforms. One thing caught his eye: Under the new approach, customers could buy only online or through call centers, types of systems that his Internet businesses had operated.

But his background didn't prepare him for the regulatory strictures of the medical marijuana business. Accustomed to developing start-ups on the fly with little capital, Mr. Rifici and Mr. Linton, another Ottawa entrepreneur who is Tweed's chairman, underestimated the money they would need by a factor of three, largely because of the government's regulatory demands. The application ran 300 pages, not including attachments. And before they could even submit applications, Tweed and other growers had to secure sites for their operations and obtain all local permissions. Applicants who passed the initial vetting then had to pass a final, two-day inspection.

The requirements are significant. Growers must have sophisticated carbon filtration systems to prevent the smell of marijuana from wafting outside. They must maintain high-security measures like biometric thumbprint readers. Employees need to pass rigorous security checks, conducted by the Royal Canadian Mounted Police, which take four to six months.

"If I knew how much regulatory overhead there would be from the beginning, I would have probably been just as excited about the industry," Mr. Rifici said. "But I might have thought that I might not be able to get there.

"Nothing like a bit of ignorance to allow you to move ahead."

The red tape was part of an effort to reform Canada's initial approach to medical marijuana. In court filings, the government suggested that the old system had become little more than a legal veneer for recreational growers, with a significant amount of marijuana making its way to illegal operations. Health Canada said users, on average, grew enough marijuana to roll 54 to 90 cigarettes a day, far beyond what they needed for personal use.

"There was big, big diversion going on," Brent Zettl, the chief executive of Prairie Plant Systems, the company that grew and distributed the government-supplied marijuana under the old system. The company is now among the newly approved growers. "They ducked behind legitimate patients and used them," he said.

Trying to Convince Doctors

Walking the vast, 425,000-square-foot factory, Mr. Rifici talks animatedly about Tweed's next steps. Just behind the new entrance of glass and shiny stainless steel, he has carved out space for a gift shop. He also hopes to lure a craft brewer into the unused portion of the factory. He wants to make 1 Hershey Drive a destination for tourists again.

Tweed is taking a subdued, almost artisanal, approach to its branding, avoiding the Cheech-and-Chong vibe of some rivals. Many of its marijuana strains are named after fusty fabrics like tweed, as well as people and places associated with such clothes. The Herringbone strain is supposed to help with depression. Bakerstreet is used to treat anxiety. Donegal is promoted as a pain reliever.

But the industry faces an uphill battle, as prominent doctors, researchers and even the Canadian Medical Association are advising against prescribing marijuana at all. Marijuana, they say, has not been through the testing and approval process required for other pharmaceuticals.

Dr. Mary-Ann Fitzcharles, a rheumatologist and professor of medicine at McGill University in Montreal, was the lead author of a widely publicized paper recommending that, without clinical evidence, marijuana should not be prescribed for rheumatoid arthritis. About 65 percent of users in Canada under the old system said they suffered from that condition. She compares the medical claims for marijuana to those once made for tobacco.

"I don't think any physician today would say: 'I suggest you take up smoking cigarettes to deal with your anxiety,' " Dr. Fitzcharles said.

So Tilray, Prairie Plant and Tweed are creating sales teams to persuade doctors to prescribe marijuana. Tweed's chief medical adviser, Dr. John Gillis, an emergency-room and chronic-pain doctor in Dartmouth, Nova Scotia, is working to develop best practices for prescribing marijuana. Christopher Murray, who worked with a Canadian agency that evaluates new drugs and medical technology, leads a "medical education and outreach" group for Tweed.

A Fine Legal Line

When Tweed shipped its first two orders directly to customers on May 5, about half of the company's management watched, partly for ceremonial reasons but mostly to make sure that its elaborate, government-mandated inventory-tracking system worked. Employees weighed the total inventory before doling out the shipments onto smaller scales calibrated to 0.01 gram. The marijuana was dropped into boxes bearing Tweed's logo and then, to meet government requirements, vacuum-packed into odor-blocking bags. Then came a final check on the scales before the two parcels left in standard courier pouches that did not bear Tweed's name.

As with many in the new industry, Tweed repeatedly cites a Health Canada forecast suggesting that the user base will grow to more than 400,000 from about 40,000. But some analysts wonder how the industry will reach such levels. Mr. Zettl is one of the few players who acknowledges that many buyers will probably be recreational users with sham prescriptions.

Like most people in the medical marijuana trade, Mr. Rifici rejected suggestions that the industry was ultimately counting on the introduction of an open, legalized market. But there is such a possibility. Justin Trudeau, the leader of the Liberal Party, has vowed to legalize marijuana if he takes power in elections scheduled for next year, and polls suggest that the idea has widespread support.

Mr. Rifici, speaking over the drone of dehumidifiers in the production facility, said that "the difference between medical marijuana and nonmedical marijuana is one of legislation." "And at the end of the day," he added, "our product is essentially high-quality marijuana under a medical platform."

http://www.eurekalert.org/pub_releases/2014-05/cafn-pat052114.php

Promising approach to slow brain degeneration in a model of Huntington's disease uncovered

Mechanism uncovered could also help preserve neuron function in Alzheimer's disease, traumatic brain injury and other neurodegenerative conditions

Research presented by Dr. Lynn Raymond, from the University of British Columbia, shows that blocking a specific class of glutamate receptors, called extrasynaptic NMDA receptors, can improve motor learning and coordination, and prevent cell death in animal models of Huntington disease. As Huntington disease is an inherited condition that can be detected decades before any clinical symptoms are seen in humans, a better understanding of the earliest changes in brain cell (neuronal) function, and the molecular pathways underlying those changes, could lead to preventive treatments that delay the onset of symptoms and neurodegeneration. "After more than a decade of research on the pre-symptomatic phase of Huntington disease, markers are being developed to facilitate assessment

of interventional therapy in individuals carrying the genetic mutation for Huntington disease, before they become ill. This will make it possible to delay onset of disease," says Dr. Raymond. These results were presented at the 2014 Canadian Neuroscience Meeting, the 8th annual meeting of the Canadian Association for Neuroscience - Association Canadienne des Neurosciences (CAN-ACN), held in Montreal, May 25-28.

The neurotransmitter glutamate has long been known to promote cell death, and its toxic effects occur through the action of a family of receptors known as the NMDARs (N-methyl-D-Aspartate ionotropic glutamate receptors). Unfortunately, treating disorders of the nervous system by blocking NMDARs has not been successful because such treatments have numerous side effects. A recent hypothesis based on work from many scientists suggests that NMDARs located in different regions at the surface of neurons may have opposite effects, which would explain why blocking all NMDARs is not a good treatment option. A synapse is a structure that allows one neuron to connect to another neuron and pass an electrical or chemical signal between them. Many receptors for neurotransmitters are located in synapses, as these are the main area where these chemical signals are transmitted. However, receptors can also be found outside the synapse, and in this case are called extra-synaptic receptors. Many recent studies have revealed that NMDARs located at synapses act to increase survival signaling and promote learning and memory, whereas extra-synaptic NMDARs shut off survival signaling, interfere with learning mechanisms, and increase cell death pathways.

Dr. Raymond and her team were able, by using a drug that selectively blocks extra-synaptic NMDARs early, before the appearance of any symptoms, to delay the onset of Huntington-like symptoms in a mouse model of the disease. These promising results could lead to new treatment avenues for Huntington patients, and delay the appearance of symptoms. "The drug we used, memantine, is currently being used to treat moderate-stage Alzheimer disease patients. Our results suggest that clinical studies of memantine and similarly-acting drugs in Huntington disease, particularly in the pre-symptomatic stage, are warranted,"says Dr. Raymond.

Extra-synaptic NMDARs have also been shown to be involved in other neurodegenerative diseases, such as Alzheimer disease, and in damage caused by traumatic brain injury and some forms of stroke. These results therefore suggest novel treatment avenues for many conditions in which neurons degenerate and die, a new way to protect neurons before the appearance of symptoms of neurodegeneration.

This research was supported by: Canadian Institutes of Health Research, Huntington Society of Canada, Cure Huntington Disease Initiative, and Michael Smith Foundation for Health Research.

http://www.eurekalert.org/pub_releases/2014-05/nlmc-mw052214.php

Mice with 'mohawks' help scientists link autism to 2 biological pathways in brain

Findings should help narrow the search for genetic contributions of autism and suggest new routes for therapy

"Aha" moments are rare in medical research, scientists say. As rare, they add, as finding mice with Mohawk-like hairstyles.

But both events happened in a lab at NYU Langone Medical Center, months after an international team of neuroscientists bred hundreds of mice with a suspect genetic mutation tied to autism spectrum disorders.

Almost all the grown mice, the NYU Langone team observed, had sideways,"overgroomed" hair with a highly stylized center hairline between their ears and hardly a tuft elsewhere. Mice typically groom each other's hair.

Researchers say they knew instantly they were on to something, as the telltale overgrooming — a repetitive motor behavior — had been linked in other experiments in mice to the brain condition that prevents children from developing normal social, behavioral, cognitive, and motor skills. People with autism, the researchers point out, exhibit noticeably dysfunctional behaviors, such as withdrawal, and stereotypical, repetitive movements, including constant hand-flapping, or rocking.

Now and for what NYU Langone researchers believe to be the first time, an autistic motor behavior has been traced to specific biological pathways that are genetically determined.

The findings, says senior study investigator Gordon Fishell, PhD, the Julius Raynes Professor of Neuroscience and Physiology at NYU Langone, could with additional testing in humans lead to new treatments for some autism, assuming the pathways' effects as seen in mice are reversible.

In the study, to be published in the journal Nature online May 25, researchers knocked out production in mice of a protein called Cntnap4. This protein had been found in earlier studies in specialized brain cells, known as interneurons, in people with a history of autism.

Researchers found that knocking out Cntnap4 affected two highly specialized chemical messengers in the brain, GABA and dopamine. Both are so-called neurotransmitters, chemical signals released from one nerve cell to the next to stimulate similar sensations throughout the body. GABA, short for gamma-aminobutyric acid, is the main inhibitory neurotransmitter in the brain. It not only helps control brain impulses, but also helps regulate muscle tone. Dopamine is a

well-known hormonal stimulant, highly touted for producing soothing, pleasing sensations.

Among the researchers' key findings was that in Mohawk-coiffed mice, reduced Cntnap4 production led to depressed GABA signaling and overstimulation with dopamine. Researchers say the lost protein had opposite effects on the neurotransmitters because GABA is fast acting and quickly released, so interfering with its action decreases signaling, while dopamine's signaling is longer-acting, so impairing its action increases its release.

"Our study tells us that to design better tools for treating a disease like autism, you have to get to the underlying genetic roots of its dysfunctional behaviors, whether it is overgrooming in mice or repetitive motor behaviors in humans," says Dr. Fishell. "There have been many candidate genes implicated in contributing to autism, but animal and human studies to identify their action have so far not led to any therapies. Our research suggests that reversing the disease's effects in signaling pathways like GABA and dopamine are potential treatment options."

The U.S. Centers for Disease Control and Prevention estimate that one in 68 American children under age 8 has some form of autism, with five times as many boys as girls suffering from the spectrum of disorders.

As part of their study, researchers performed dozens of genetic, behavioral, and neural tests with growing mice to isolate and pinpoint where Cntnap4 acted in their brains, and how it affected chemical signaling among specific interneuron brain cells, which help relay and filter chemical signals between neurons in localized areas of the brain.

They found that Cntnap4 in mature interneurons strengthened GABA signaling, but did not do so in younger interneurons. When researchers traced where Cntnap4 acted in immature brain cells, Dr. Fishell says tests showed that it stimulated "a big bolus of dopamine."

As part of testing to confirm the hereditary link among Cntnap4, the two pathways, and grooming behaviors, researchers exposed young mice with normal levels of Cntnap4, who did not groom each other, to mature mice with and without Cntnap4. Only mature mice deficient in Cntnap4 preened the hairstyle on other mice. Further tests in young mice without Cntnap4 showed that other, mature mice with normal amounts of Cntnap4 largely let them be, without any particular grooming or hairstyle.

Dr. Fishell and his team plan further analyses of how GABA and dopamine production changes as brain cells mature, and precisely what cellular mechanisms are involved in autism. Their goal is to control and rebalance any biological systems that go awry, as a possible future therapy for the disease.

Funding support for the study was provided by the Simons Foundation, the National Institute for Mental Health, and the National Institute of Neurological Disorders and Stroke, both members of the US National Institutes of Health. Corresponding federal grant numbers are R01 NS081297, R01 MH071679, R01 NS074972, P01 NS074972, R01 NS036362, R01 DA033811, NS30989, NS30989, and NS50220. Study funding was also supported by grants from the Attilio and Olympia Ricciardi Research Fund, the Israel Science Foundation, as well as through postdoctoral fellowships from the Patterson Trust and Roche Inc., the New York State NYSTEM initiative, and the Canadian Institutes of Health Research.

Besides Dr. Fishell, other NYU Langone researchers involved in this study were Theofanis Karayannis, DPhil; Edmund Au, PhD; Jyoti Patel, PhD; Ilya Kruglikov, PhD; Bernardo Rudy, MD, PhD; Margaret Rice, PhD; Charles Hoeffer, PhD; and Richard Tsien, DPhil. Additional research support was provided by Sander Markx, MD; Laura Rodriguez-Murillo, PhD; and Maria Karayiorgou, MD, at Columbia University in New York City; Joseph Glessner, PhD, at the Children's Hospital of Philadelphia; Richard Delorme, PhD; Hakon Hakonarson, MD, PhD; Guillaume Huguet, PhD; and Thomas Bourgeron, PhD, at L'Institut Pasteur in Paris, France; Delphine Heron, MD; and Boris Keren, MD, at the Groupe Hospitalier La Pitié-Salpêtrière, also in Paris, France; and Aaron Gordon, PhD; and Elior Peles, PhD, at the Weizmann Institute of Science in Rehovot, Israel.

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Macrolide Benefit Unclear in Kids With Mycoplasma Pneumonia

Macrolide treatment of Mycoplasma pneumoniae may or may not benefit children with community-acquired lower respiratory tract infection (CA-LRTI), according to an article published in the June issue of Pediatrics.

Larry Hand

Eric Biondi, MD, from the Department of Pediatrics, University of Rochester, New York, and colleagues conducted a systematic review and meta-analysis of published articles on observational and randomized trials comparing macrolide, tetracycline, or quinolone class antibiotics with spectrum of activity for M pneumonia with placebo or other antibiotics that lacked spectrum of activity for M pneumonia in children younger than 18 years who had CA-LRTI.

The researchers identified 17 trials involving 4294 patients. They identified 9 studies (723 patients) with enough detail to compare M pneumonia spectrum and nonspectrum treatment in children with CA-LRTI secondary to M pneumonia. Of those 9 trials, nearly all prospective studies found no clinical benefit, and for the ones that suggested a statistical decrease in fever duration, the decrease was "not necessarily clinically relevant," the researchers write.

They conducted a meta-analysis of 5 randomized controlled trials, and 4 of those studies did not find a benefit from M pneumonia treatment. The meta-analysis "suggests a small treatment benefit in patients with CA-LRTI secondary to M.

pneumonia," the researchers write. However, they point out that the pooled effect favoring treatment resulted primarily from a single randomized trial that examined macrolide treatment effects and included children with upper respiratory tract infections.

"Our systematic review provides insufficient evidence to support conclusions about the efficacy of macrolide treatment of CA-LRTI due to M. pneumoniae in children," the researchers conclude.

They call for more research with high-quality prospective studies that address potential confounding, mixed infections, timing of intervention, and testing modalities.

Uncertainty, Both Ways

In an accompanying editorial, Andrew A. Colin, MD, from the Division of Pediatric Pulmonology and Department of Pediatrics at the Miller School of Medicine, University of Miami, Florida, and colleagues write that setting the parameters of such studies would be "a colossal undertaking indeed."

Children with M pneumoniae infections "mostly recover spontaneously, and it is difficult to assess how intervention and timing thereof within the course of the infection can be factored in when studying the results of therapies."

The editorialists conclude that the new study "further buttresses the uncertainty of the antibiotic treatment" of CA-LRTI secondary to M pneumonia but does not provide guidance for physicians in daily practice. "[B]y no means should it be construed as evidence against the use of macrolide (or other appropriate) antibiotics in bona fide [M pneumonia] cases."

The authors and editorialists have disclosed no relevant financial relationships.

Pediatrics. 2014;133:1081-1090, 1124-1125.

http://www.bbc.com/news/magazine-27537142

Spurious correlations: Margarine linked to divorce?

A website set up by a student at Harvard teaches us to look carefully at statistics. And it's fun at the same time.

By James Fletcher BBC News

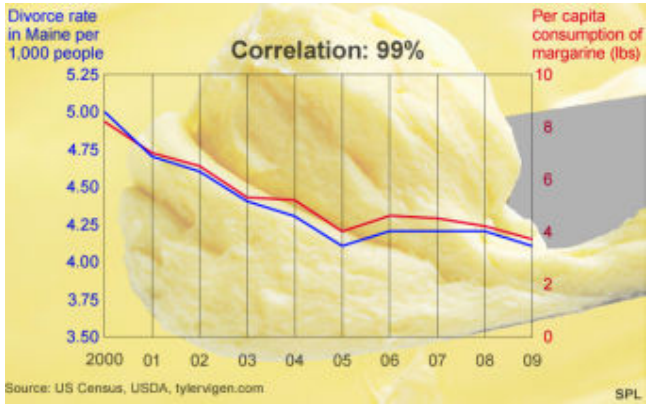
"Margarine consumption linked to divorce." If you saw that headline on a newspaper or website, what would you think?

What if you read a little further and found a compelling graph showing the rates of divorce and margarine consumption tracking each other closely over almost 10 years.

Tempted to believe there could be a link?

"Maybe when there's more margarine in the house it's more likely to cause divorce," muses Tyler Vigen, "or there's a link with some of the molecules in margarine or something."

Vigen is the man behind the margarine graph, which he published on his website Spurious Correlations. The name gives the game away - he's a statistical provocateur.



"I've seen a lot of headlines, especially sensationalist ones - 'Scientists find a connection between x and y,' he says."

"In a lot of those situations there might be a correlation, but it's really important for us to be critical about whether there's a causal mechanism."

One of the golden rules of statistics is that correlation does not equal causation. Just because the movements of two variables track each other closely over time doesn't mean that one causes the other.

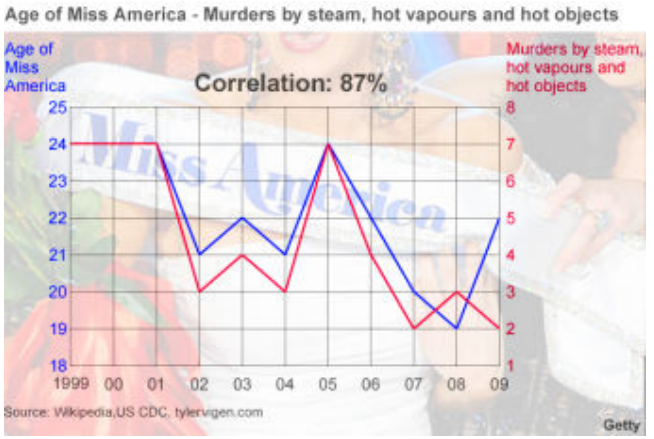
To make this important, but somewhat dry, point more accessible, Vigen, a criminology student at Harvard Law School, wrote a computer programme to mine datasets for statistical correlations. He posts the funniest ones to Spurious Correlations.

"What's kind of fun about it is it allows people to be their own scientist for a few minutes, because they get to come up with their own hypothesis," he says.

The site contains plenty of raw material to test out your ability to come up with a creative causal mechanism.

What links rising per capita cheese consumption to the number of people who died by becoming tangled in their bedsheets?

Why do murders by steam, hot vapours and hot objects rise and fall with the age of the winner of the Miss America beauty pageant?



And how does the number of films Nicholas Cage appears in each year influence the number of female editors of the Harvard Law Review?

"We think about that for a second, and realise that we have no basis for that in

reality," says Vigen. "There's just nothing that can confirm that for us and we can kind of reject our own hypothesis outright."

Real world examples of the difference between correlation and causation abound.

A classic is that in summer, ice cream sales and murder rates rise.

The two are correlated, but it's easy to see that neither causes the other.

Perhaps there's a third variable - like hot weather - that causes both?

More seriously, when hormone replacement therapy became commonplace, doctors noticed that women taking HRT seemed less likely to get coronary heart disease.

Some doctors suggested a causal relationship - that HRT lowered the risk of heart disease.

Again it turned out that there was a third variable at play. Women who were taking HRT were more likely to come from higher socio-economic groups, with healthier diet and exercise habits.

It's this that lowered the risk of heart disease.

In the end, other tests showed that HRT actually raised the risk slightly.

Vigen's site has attracted lots of attention on social media, where making fun of correlations is a healthy meme. A quick search turns up graphs "proving" Facebook caused the Greek debt crisis, or that a pirate shortage "caused" global warming.

Spurious Correlations goes further in illustrating the pitfalls of our data-rich age.

One is that if you throw enough processing power at a large data set you can unearth huge numbers of correlations.

Many will be statistically significant, meaning that they're unlikely to have occurred by chance alone.

But causal relations, where a change in one variable causes a change in the other, are much harder to find.

Another pitfall is the seductive power of graphs.

Numbers in datasets can be hard to grasp, but show someone two lines moving up or down in apparent unison and you're halfway to convincing them that one causes the other.

"A lot of my charts illustrate where there isn't a statistically significant correlation but it looks like there is because of how I plotted them on a graph," he says.

Take the graphs of Nicholas Cage's film appearances - there are several on Vigen's website.

Cage's appearances only vary between zero and four each year, but by choosing the scale carefully they can be made to track other variables which rise and fall by millions.

"When you only have maybe 10 (data) points to go by, it's not that hard to find overlapping lines that curve or vary together," says Vigen.

So what are Tyler Vigen's tips to make sure the statistical wool isn't being pulled over your eyes?

Be critical of statistics that you see

Look for a causal link or mechanism

Demand a little bit of scientific rigour in showing that there's a strong, statistically significant correlation

Something to bear in mind next time a sensational headline catches your eye.