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# First-in-human clinical trial of new targeted therapy drug reports promising responses for multiple cancers

***Significant durable disease control seen in patients with lung and thyroid cancers harboring the RET oncogene***

A phase I, first-in-human study led by The University of Texas MD Anderson Cancer Center reveals for the first time, an investigational drug that is effective and safe for patients with cancers caused by an alteration in the receptor tyrosine kinase known as RET. The drug appears to be promising as a potential therapy for RET-driven cancers, such as medullary and papillary thyroid, non-small cell lung, colorectal and bile duct cancers, which have been historically difficult to treat.

The oral drug, BLU-667, is being investigated in a multi-center, open label trial. The pre-clinical and early clinical validation are published in April 15 online issue of Cancer Discovery. The results from the trial were presented April 15 at the American Association for Cancer Research Annual Meeting 2018 in Chicago.

"There is a critical un-met need for effective drugs against cancers that have the RET alteration, as there are no highly potent inhibitors currently approved specifically for these RET-driven cancers," said Vivek Subbiah, M.D., Assistant professor of Investigational Cancer Therapeutics. "The current treatments for these cancers are limited to traditional chemotherapy and earlier generations of multiple kinase inhibitors. These options have had limited success with often considerable side effects that significantly impact the patient's quality of life."

Subbiah's study is investigating BLU-667 as a novel precision-targeted drug that, through a proof-of-concept trial, has shown promising activity and disease control as a highly selective RET inhibitor. The drug targets RET-altered cancers with fewer side effects affecting non-cancerous organs.

RET is linked to half of all medullary thyroid cancers, 20 percent of papillary thyroid cancers and 1 to 2 percent of non-small cell lung cancers. Subbiah's team followed 43 patients with advanced tumors not eligible for surgery. The investigation also studied 26 patients with medullary thyroid cancer, 15 with non-small cell lung cancer and two with other RET-driven cancers.

"Tumor reductions and durable responses were observed in most patients, especially those patients whose cancer progressed with chemotherapy and multi-kinase inhibitors," said Subbiah. "Our study reported an overall response rate of 37 percent for RET-driven cancers, with responses of 45 percent for non-small cell lung cancer and 32 percent for medullary thyroid."

BLU-667 was chosen for investigation because it is 100 times more selective for RET than other kinases tested, and has proved effective in stopping genetic mutations known as gatekeepers, which have been tied to resistance to multiple kinase therapy.

"Overall, the data show the precision targeted therapy with next-generation kinase inhibitors can have a powerful impact for patients with RET-driven cancers," said Subbiah. "By offering a highly selective medicine tailored for this oncogenic driver, we hope this new therapy will enable patients to benefit from the recent advances in genomic profiling that have revolutionized treatment options for patients with kinase-driven diseases."

*Another MD Anderson researcher also involved is Mimi Hu, M.D., Endocrine Neoplasia and Hormonal Disorders. Other institutions involved included Massachusetts General Hospital, Boston; Blueprint Medicines Corp., Cambridge, Mass.; Abramson Cancer Center, University of Pennsylvania, Philadelphia; Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center; The Knight Cancer Institute, Oregon Health & Science University; and Vall d'Hebron Institute of Oncology, Barcelona. The study was funded by Blueprint Medicines Corp., which developed BLU-667.*

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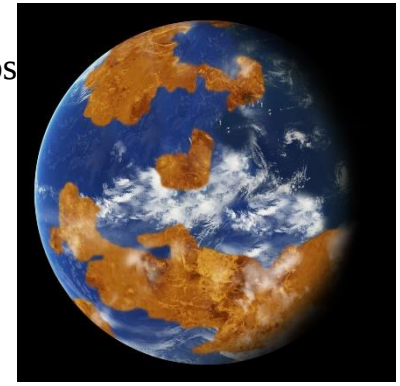
# Evidence mounts for habitability of Venus-like worlds

***Climate models show exoplanets like Venus could hold oceans under the right conditions.***

**Richard A. Lovett reports.**

Venus-like exoplanets might not be super-heated hothouses, say scientists. Evidence is mounting that even Venus itself could have

supported liquid oceans as recently as 750 million years ago, says Michael Way, an atmospheric scientist at NASA's Goddard Institute for Space Studies in New York City.



***Venus may once have held watery oceans.*** **NASA**

Venus is dry now, but based on isotope ratios of hydrogen in its present atmosphere, scientists can calculate how much water it once had, Way said at a NASA-sponsored symposium called "Environments of Terrestrial Planets Under the Young Sun: Seeds of Biomolecules," in Greenbelt, Maryland.

Based on these ratios, it appears that Venus has lost at least 99.9 percent of its water, which means it might once have had enough to cover it to a depth of several hundred meters. Exactly how much is a bit vague (estimates vary by a factor of a hundred) but either way, Way says, there would have been enough to form sizeable oceans or at least lakes.

Assuming that the early atmosphere of Venus was similar to Earth's (not unlikely, because the two planets are so close in size and composition that they are often viewed as twins), he says, it's possible to use climate models to calculate the Venusian climate as the Sun steadily warmed and Venus moved from receiving about 35 percent more solar energy than the modern Earth to 90 percent more.

The result, Way says, is surprising: even if Venus started with very little water, it would not only have retained it but would have been quite temperate, even as recently as 715 million years ago.

A number of factors appear to play into this remarkable result. One is that Venus is rotating slowly, with a Venusian day lasting nearly as long as 117 Earth days. This slow rotation would have allowed a younger, potentially habitable, Venus to build up a layer of clouds on its sunward side, reflecting a lot of solar energy back into space. On a faster rotating Venus-like world, the clouds wouldn't form until afternoon, when the sun is no longer high enough to block as much solar energy.

What this means for exoplanets is that the habitability of Venus-like worlds close to their suns might depend on their rotation rates – something that exoplanet hunters can't yet determine.

"It will be ten to fifteen years before we get rotation rate data on these exoplanets," Way says, "but it will probably tell us a lot."

His model also assumes that the early Venus (and similar exoplanets) had some form of tectonics that, through rock-weathering processes, could recycle volcano-produced carbon dioxide from the atmosphere back into the interior. Otherwise, the planet-warming gas would build up to a point where all of the water evaporates and the planet goes into a superheated state like modern Venus, where surface temperatures are on the order of 450°C.

In fact, Way suggests, the end of Venusian habitability may have been caused not by the slow warming of the Sun, but by massive volcanism, which appears to have covered 80-85 percent of the Venusian surface about 750 million years ago, in the process releasing tremendous amounts of carbon dioxide. "The planet can handle increased [solar energy]," he says. "Probably something else happened, and it probably has to do with the resurfacing events."

Matthew Weller, a planetary scientist from the Institute for Geophysics at the University of Texas at Austin, who has studied Venusian tectonics, agrees. "The picture that is emerging between Michael's stuff (atmosphere) and my stuff (interior-to-atmosphere) is that the potential for liquid water and habitability depends on far more than just the distance to the host star," he says.

Figuring all of this out for exoplanets, he adds, means paying more attention to Venus. "It's the forgotten planet," he says.

***http://bit.ly/2qJ2Ttj***

## New Invention Detects Cancer in Seconds

***The code has been copied to your clipboard.***

**Elizabeth Lee**

Austin, Texas — Technology is being developed in Austin, Texas, to make cancer detection faster and tumor removal more precise. A device

called the MasSpec Pen can detect cancer with just one touch, researchers said.

“Well, it’s a game changer because I was doing a case the other day with a surgeon, and we had to wait an additional two hours because the current method takes that long,” said Aydin Zahedivash, medical student and co-creator of the MasSpec Pen.

He says the pen can deliver results within 20 seconds and is much less invasive for the patient than the traditional method of diagnosis.

No biopsy needed

“That process usually will involve taking out some of the tissue, which means cutting it from a patient. Our technology can detect cancer inside of a tissue without cutting it or altering it,” Zahedivash said.

During surgery, a drop of water on the pen pulls molecules from the tissue in question. An instrument called the mass spectrometer then analyzes the water with the molecules to determine whether cancer is present in the tissue. It adds precision to detecting the disease.

In seconds, surgeons will know what part of the tissue to extract, how much to cut, and what not to touch so healthy tissue is not damaged.

“We’ve done testing on human tissues that have been taken out of patients and those have shown 96 percent accuracy detecting cancer from non-cancer,” Zahedivash said.

Rapid development

New available technologies have allowed an interdisciplinary team to develop the MasSpec Pen in 2½ years. The team 3-D printed the prototype, allowing the creators to rapidly develop a design that worked.

Zahedivash said within the year, the MasSpec Pen will be tested in surgery at the Dell Medical School at the University of Texas at Austin.

There are also plans to test the technology at the MD Anderson Cancer Center and Baylor College of Medicine in Houston.

The device would require approval from the U.S. Food and Drug Administration before becoming widely available.

***https://bbc.in/2HDufdZ***

## Ketamine has 'fast-acting benefits' for depression

***Ketamine has "shown promise" in the rapid treatment of major depression and suicidal thoughts, a US study says.***

Ketamine has a reputation as a party drug but is licensed as an anaesthetic.

The study found use of the drug via a nasal spray led to "significant" improvements in depressive symptoms in the first 24 hours.

The Royal College of Psychiatrists said it was a "significant" study that brought the drug "a step closer to being prescribed on the NHS".

The report by researchers from Janssen Research and Development, a Johnson and Johnson company, and Yale School of Medicine, is the first study into ketamine as a treatment for depression that has been done by a drug company. It is being published in the American Journal of Psychiatry. The trial looked at 68 people at imminent risk of suicide.

All patients were treated with a stay in hospital and anti-depressants.

In addition, half were given ketamine in the form of esketamine (part of the ketamine molecule) in a nasal spray and half were given a placebo.

The study found those using esketamine had a much greater improvement in depression symptoms at all points over the first four weeks of treatment. However, at 25 days the effects had levelled out.

The study's authors suggest it could offer an effective rapid treatment for people severely depressed and at imminent risk of suicide and could help in the initial stages of treatment, as most anti-depressants take four to six weeks to become fully effective. The nasal spray is now undergoing phase three trials before it can be licensed for treatment.

**Potential for abuse**

There were no reports of esketamine dependence or misuse in the trial but the authors warn that more research is needed on the potential for abuse of ketamine and say these should be looked at during subsequent trials. Scientists in the UK are also studying ketamine as a treatment for depression taken intravenously.

Dr James Stone, from the Royal College of Psychiatrists, told the BBC the "interesting" US study confirmed the findings from successful studies into intravenous ketamine.

"The main reason for its significance is because this is being developed by a drug company and it's potentially quite likely that this medication might become available as a treatment available on the NHS for depression."

**'Severe depression'**

He said because it was being given as a nasal spray it was "much easier to administer" than intravenous ketamine and was "potentially quicker to give, so it means more people can be dosed at the same time" and you need less equipment.

Dr Stone said if it did go on to be prescribed on the NHS it would be aimed at people with severe depression as a second or third line of treatment if other drugs haven't worked and could be used for people instead of electroconvulsive therapy.

Prof Mitul Mehta from King's College told the BBC it was an "exciting" study. "All the studies to date have been looking at intravenous use - there are some people who have explored oral ketamine but that doesn't appear to be as successful as intravenous so intranasal seems to be a really good halfway-house.

"It enters the body relatively quickly - it's not as fast as going straight into your bloodstream but not as slow as via the stomach and it's reasonably easy to control how much you give to a person. In that respect this is a really important study."

But he said far bigger studies are needed to look out for any rare side-effects.

**Prescribed off licence**

Because ketamine is licensed to be used by doctors as an aneasthetic it can be prescribed off licence for depression. This is happening in private clinics in the US and the UK. But to be prescribed on the NHS, it would need to be licensed to be used as a treatment for depression.

In the UK, doctors have been trialling ketamine to treat depression since 2011.

Dr Rupert McShane, who has led a trial in Oxford, says ketamine can work on patients with depression "where nothing has helped before".

Last year he called for the use of ketamine to treat depression to be rolled out. However, he called for a national registry to monitor its use.

***https://bbc.in/2qL35rj***

## Australia flesh-eating ulcer 'epidemic' a mystery, doctors say

***Doctors in Australia have called for urgent research into why a flesh-eating ulcer has become a "worsening epidemic" in the state of Victoria.***

***Victoria has seen a spike in recent cases of the Buruli ulcer*** **Daniel O'Brien**

Local cases of Buruli ulcer, a skin disease most commonly found in Africa, have surged by 400% in the last four years, experts say.

Infections have also become more severe and spread to new areas.

Doctors do not know how to prevent the disease, which is caused by bacteria that breaks down tissue.

A record 275 new infections were recorded the state last year, marking a 51% increase on 2016.

Infectious diseases expert Dr Daniel O'Brien said cases of the Buruli ulcer, or Mycobacterium ulcerans disease, had become "frighteningly more common and also more severe" in the region.

It was unclear why the ulcer, typically found in tropical areas, had emerged in the temperate climate of Victoria, he said.

**What is the Buruli ulcer?**

- ***A skin disease caused by the bacterium Mycobacterium ulcerans.***
- ***The bacteria emits toxins that destroy skin cells, small blood vessels and the fat under the skin, leading to ulcers forming and skin loss.***

- ***The ulcer gets bigger with time and can lead to permanent disfigurement or disability.***
- ***Usually affects limbs but can also be found on the face and body.***
- ***Doctors do not know how the disease is transmitted to humans but it's believed to arise from the environment and soil.***
- ***There are also theories that mosquitoes can carry the bacteria.***

Writing in the Medical Journal of Australia, doctors have called for government funding to research the disease and its causes.

"No one understands what's happening and what's driving this epidemic," Dr O'Brien, a co-author, told the BBC. "We can offer clues but not definitive advice. It's a mystery."

He said some theories involved factors such as rainfall, soil type and wildlife.

Last year, authorities found traces of the bacteria in local possum faeces.

***The Buruli ulcer attacking a patient's knee*** **Ella Crofts**

"The problem is, we don't have the time to sit around and pontificate about it - the epidemic has reached frightening proportions," he said.

The ulcers are difficult to treat and patients often experience a recovery period of between six and 12 months.

Many people also have to undergo reconstructive surgery, Dr O'Brien added.

Victorian health authorities say they have spent more than A$1m (£550,000; $780,000) on researching the disease, and have started education campaigns to raise awareness about it.

Until a few years ago, infections were more commonly reported from tropical regions in Queensland with occasional cases in other states.

The disease is more commonly found in rural West Africa, Central Africa, New Guinea, Latin America and tropical regions of Asia.

In the developing world, the disease is associated with wetlands and stagnant water, however in Australia cases have largely been reported from coastal regions.

***https://nyti.ms/2J99QdM***

# Friendship's Dark Side: 'We Need a Common Enemy'

***Researchers who explore the deep nature of friendship admit the bond can have its thorns, bruise spots and pesticide traces***

**By NATALIE ANGIER APRIL 16, 2018**

As a rule, friendship is considered an unalloyed good, one of life's happy-happies, like flowers and fresh fruit. "Report: It Would Probably Be Nice Having Friends," read a recent headline in The Onion. Ha ha! Of course it's "kind of fun" and "pretty cool" to "have a few select people in your life to do stuff with on a regular basis."

**Credit Keith Negley**

Most people can name at least half a dozen people they view as reasonably good friends. The only society where people don't have any friends, according to Daniel Hruschka, an evolutionary anthropologist at Arizona State University, is found in the science fiction of C.J. Cherryh's "Foreigner" series.

Yet researchers who explore the deep nature of friendship admit the bond can have its thorns, bruise spots and pesticide traces.

Take the new evidence that people choose friends who resemble themselves, right down to the moment-to-moment pattern of blood flow in the brain. The tendency toward homophily, toward flocking together with birds of your inner and outer feather, gives rise to a harmonious sense of belonging and shared purpose, to easy laughter and volumes of subtext mutually, wordlessly, joyfully understood.

But homophily, researchers said, is also the basis of tribalism, xenophobia and racism, the urge to "otherize" those who differ from you and your beloved friends in one or more ways.

The impulse can yield absurd results. One recent study from the University of Michigan had subjects stand outside on a cold winter day and read a brief story about a hiker who was described as either a "left-

wing, pro-gay-rights Democrat" or a "right-wing, anti-gay-rights Republican."

When asked whether the hypothetical hiker might feel chilly as well, participants were far more likely to say yes if the protagonist's political affiliation agreed with their own. But a political adversary — does that person even have skin, let alone a working set of thermal sensors?

"Why must it be the case that we love our own and hate the other?" Nicholas Christakis of Yale University said. "I have struggled with this, and read and studied a tremendous amount, and I have mostly dispiriting news. It's awful. Xenophobia and in-group bias go hand-in-hand."

Game theory models predict it, real-life examples confirm it. "In order to band together, we need a common enemy," Dr. Christakis said.

Fortunately, he added, no model insists that the out-group must be exterminated or otherwise eliminated from the scene. "It's possible to treat the out-group with mild dislike or even grudging respect," he said. "Cultivating in-group distinctiveness does not require that the other must be killed."

Nevertheless, even the ordinary business of making friends is an exclusionary act, a judgment call, and therefore threaded with the potential for pain.

"A friendship is always a little bit of a conspiracy," said Alexander Nehamas, a professor of philosophy at Princeton. "We two are here, they are over there, and we're going to do our thing whether they want us to or not." And if they try to join us, we can say, no, sorry, that seat is taken. We're saving it for a friend.

Who may not return the favor. Abdullah Almaatouq of the Massachusetts Institute of Technology and his colleagues recently showed that people are poor judges of who their friends are.

When the researchers asked 84 college students to identify which of their classmates qualified as friends, the researchers found that in half the cases, those labeled friends failed to reciprocate the designation.

Other studies have shown similar discordances or worse, with one survey revealing that 66 percent of supposed friendships were cases of unrequited like.

Friendships are also surprisingly fragile. Based on a detailed survey of 540 participants, researchers at Oxford University determined that people had a falling out with a member of their social circle about once every 7.2 months, or nearly two times annually, and that a year later 40 percent of those ruptures remained unhealed.

The overall rates of friendship conflict did not differ between men and women, but women were more likely to clash with close friends, to express feelings of anguish over the breakup, and to be more demanding of evidence of remorse before reconciling.

Sure, love may mean never having to say you're sorry. But friendship is a stricter taskmaster, and sorry may not be enough.

***http://bit.ly/2JZPt4b***

## 'Mono' virus linked to 7 serious diseases

### *Epstein-Barr virus may affect health in more ways than known*

CINCINNATI - A far-reaching study conducted by scientists at Cincinnati Children's reports that the Epstein-Barr virus (EBV)--best known for causing mononucleosis--also increases the risks for some people of developing seven other major diseases.

Those diseases are: systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), celiac disease, and type 1 diabetes. Combined, these seven diseases affect nearly 8 million people in the U.S.

Study results published April 12 in the journal Nature Genetics. The project was led by three scientists: John Harley, MD, PhD, Director of the Center for Autoimmune Genomics and Etiology (CAGE) at Cincinnati Children's and a faculty member of the Cincinnati VA Medical Center; Leah Kottyan, PhD, an immunobiology expert with CAGE; and Matthew Weirauch, PhD, a computational biologist with

the center. Critical contributions were provided by Xiaoting Chen, PhD, and Mario Pujato, PhD, both also in CAGE.

The study shows that a protein produced by the Epstein-Barr virus, called EBNA2, binds to multiple locations along the human genome that are associated with these seven diseases.

Overall, the study sheds new light on how environmental factors, such as viral or bacterial infections, poor diet, pollution or other hazardous exposures, can interact with the human genetic blueprint and have disease-influencing consequences.

"Now, using genomic methods that were not available 10 years ago, it appears that components made by the virus interact with human DNA in the places where the genetic risk of disease is increased," Harley says. "And not just for lupus, but all these other diseases, too."

The full impact of this study could take years to explore. Here are some of the initial implications:

**New concern about the 'kissing disease'**

EBV is a strikingly common virus. In the US and other developed nations, more than 90 percent of the population becomes infected by age 20. In less-developed nations, 90 percent of people become infected by age 2. Once infected, the virus remains in people for their entire lives.

Mononucleosis, which causes weeks of extreme fatigue, is the most common illness caused by EBV. Mono was nicknamed the "kissing disease" years ago because the virus spreads primarily via contact with saliva.

Over the years, scientists have linked EBV to a few other rare conditions, including certain cancers of the lymphatic system. Harley, who has devoted much of his career to studying lupus, found possible connections between lupus and EBV years ago. That work includes proposing mechanisms that the immune system uses in response to the virus that lead to lupus, and showing that children with lupus almost always are infected with EBV.

Today's study adds weight to those lupus findings and adds six more well-known diseases to the list.

"This discovery is probably fundamental enough that it will spur many other scientists around the world to reconsider this virus in these disorders," Harley says. "As a consequence, and assuming that others can replicate our findings, that could lead to therapies, ways of prevention, and ways of anticipating disease that don't now exist." So far, no vaccine exists that will prevent EBV infection.

"I think we've come up with a really strong rationale for encouraging people to come up with more of an effort," Kottyan says. "Some EBV vaccines are under development. I think this study might well encourage them to push forward faster and with rededicated effort."

**How EBV hijacks our immune system**

When viral and bacterial infections strike, our bodies respond by commanding B cells within our immune systems to crank out antibodies to battle the invaders. However, when EBV infections occur, something unusual happens.

The EBV virus invades the B cells themselves, re-programs them, and takes over control of their functions. The Cincinnati Children's research team has discovered a new clue about how the virus does this, a process that involves tiny proteins called transcription factors.

Our bodies have about 1,600 known transcription factors at work within our genome. Each cell uses a subset of these to become what they are and to respond to their environment. These proteins constantly move along the strands of our DNA, turning specific genes on and off to make sure cells function as expected.

However, when the transcription factors change what they do, the normal functions of the cell can also change, and that can lead to disease.

The Cincinnati Children's team suspects that the EBNA2 transcription factor from EBV is helping change how infected B cells operate, and how the body responds to those infected cells.

The new paper shows that seven seemingly unrelated disease states actually share a common set of abnormal transcription factors, each affected by the EBNA2 protein from the Epstein-Barr virus. When these EBNA2-related clusters of transcription factors attach themselves

to one portion of the genetic code, the risk of lupus appears to rise. When those same transcription factors land on another part of the code, the risk of multiple sclerosis appears to rise. And so on.

"Normally, we think of the transcription factors that regulate human gene expression as being human," Kottyan says. "But in this case, when this virus infects cells, the virus makes its own transcription factors, and those sit on the human genome at lupus risk variants (and at the variants for other diseases) and that's what we suspect is increasing risk for the disease."

**New leads emerge for improving treatment**

It remains unclear how many cases of the seven diseases listed in the study can be traced to prior EBV infection. More genomic analyses involving many more patients with these diseases will be required to make reliable estimates.

"The impact of the virus is likely to vary across the diseases," Harley says. "In lupus and MS, for example, the virus could account for a large percentage of those cases. We do not have a sense of the proportion in which the virus could be important in the other EBNA2-associated diseases."

However, the breakthrough identification of specific transcription factors connected to EBV infections opens new lines of study that could accelerate efforts to find cures.

"This same cast of characters is a villain in multiple immune-related diseases," Weirauch says. "They're playing that role through different ways, and doing it at different places in your genome, but it's the same sinister characters. So if we could develop therapies to stop them from doing this, then it would help multiple diseases."

A number of compounds--some experimental, some approved as medications for other conditions--already are known to be capable of blocking some of the high-risk transcription factors listed in the paper, Weirauch says. Teams at Cincinnati Children's have begun deeper studies of some of these compounds.

**Findings go far, far beyond EBV**

While the EBV-related findings involved more than 60 human proteins linked to seven diseases, the Cincinnati Children's research team already has taken a huge next step. They applied the same analytic techniques to tease out connections between all 1,600 known transcription factors and the known gene variants associated with more than 200 diseases.

The results of that massive cross-analysis also appear in today's study. Intriguing associations were documented involving 94 conditions.

"Our study has uncovered potential leads for many other diseases, including breast cancer," Harley says. "We cannot possibly follow up on all of these, but we are hoping that other scientists will."

After devoting decades of research to hunting down the causes of lupus, Harley says this study represents the most important discovery of his career. "I've been a co-author in almost 500 papers. This one is more important than all of the rest put together. It is a capstone to a career in medical research," he says.

**Software behind discoveries to be made public**

Detecting and tracking the activities of these transcription factors took years of work involving dozens of laboratory and computational experts. The project required gathering massive sets of genetic data, then analyzing every genetic change affecting the activity of the virus. Doing this required creating two new algorithms, called RELI and MARIO, which were developed at Cincinnati Children's by Weirauch and colleagues. Both software tools and a related website will be made publicly available.

"We are going to great lengths to not only make the computer code available, but all of the data and all of the results," Weirauch says. "We think it's an interesting approach that could have implications for many diseases, so we're contacting experts on the various diseases and sharing the results and seeing if they want to collaborate to follow up on them."

*Funding support for the research came from: a Kirkland Scholar Award; the Cincinnati Children's Research Foundation; the National Institutes of Health, (R21HG008186, R01AI024717, U01HG008666, U01AI130830, P30AR070549, R24HL105333, R01DK107502, UL2TR001426, AR042060, AI31584, R01DK107502, DP2GM119134, P30AR070549,*

*P30DK078392); Lupus Research Alliance "Novel Approaches"; the Cincinnati Children's Center for Pediatric Genomics; the US Department of Veterans Affairs (I01BX001834).*

***GLOSSARY OF TERMS***

***What is the Epstein-Barr virus?***

*The Epstein-Barr virus (EBV) is an extremely common virus usually spread by saliva. EBV causes mononucleosis, and has been associated with a growing number of other diseases. A study led by Cincinnati Children's, published today in* Nature Genetics, *adds seven diseases to that list.*

***What is mononucleosis?***

*Also known as "mono," and nicknamed the "kissing disease," the symptoms of this condition include extreme fatigue, fever, sore throat, head and body aches, swollen lymph nodes in the neck and armpits, swollen liver or spleen or both, and rash, according to the Centers for Disease Control and Prevention. Most people get better in two to four weeks. However, some people may feel fatigued for several more weeks.*

***What is a B cell?***

*B cells are a type of white blood cell found in the immune system. These cells produce antibodies in reaction to infections by bacteria, viruses and other invaders. Epstein-Barr virus infects a small proportion of these cells.*

***What is a transcription factor?***

*Transcription factors are proteins that "turn on and turn off" genes. These proteins help direct cell growth, division, and death. They also control cell migration and organization. There are about 1,600 known human transcription factors that do their work along the human genome. These proteins change the expression of genes to make RNA, which in many cases results in forming other proteins that change how cells form and function.*

***What is a DNA variant?***

*The DNA genome of every person contains over 3 billion DNA bases. Most of the bases are exactly the same for every person. However, about 1 percent of the bases can be different and these create diversity between people. The variants can change the way proteins are made or change the regulatory processes that lead to protein production.*

***What is a genetic risk variant?***

*When a DNA variant is known to increase risk for a disease, it is called a genetic risk variant. Some variants increase risk for multiple diseases, and some variants are specific to a single disease.*

***http://bit.ly/2He0X6h***

## Dinosaurs ended -- and originated -- with a bang!

### *Key expansion of dinosaurs was also triggered by a crisis*

It is commonly understood that the dinosaurs disappeared with a bang - wiped out by a great meteorite impact on the Earth 66 million years ago.

But their origins have been less understood. In a new study, scientists from MUSE - Museum of Science, Trento, Italy, Universities of Ferrara and Padova, Italy and the University of Bristol show that the key expansion of dinosaurs was also triggered by a crisis - a mass extinction that happened 232 million years ago.

In the new paper, published today in *Nature Communications*, evidence is provided to match the two events - the mass extinction, called the Carnian Pluvial Episode, and the initial diversification of dinosaurs.

***A life-scene from 232 million years ago, during the Carnian Pluvial Episode after which dinosaurs took over. A large rauisuchian lurks in the background, while two species of dinosaurs stand in the foreground, and some rhynchosaurs sit on the logs to the left. Based on data from the Ischigualasto Formation in Argentina.*© Davide Bonadonna.**

Dinosaurs had originated much earlier, at the beginning of the Triassic Period, some 245 million years ago, but they remained very rare until the shock events in the Carnian 13 million years later.

The new study shows just when dinosaurs took over by using detailed evidence from rock sequences in the Dolomites, in north Italy - here the dinosaurs are detected from their footprints.

First there were no dinosaur tracks, and then there were many. This marks the moment of their explosion, and the rock successions in the Dolomites are well dated. Comparison with rock successions in Argentina and Brazil, here the first extensive skeletons of dinosaurs occur, show the explosion happened at the same time there as well.

Lead author Dr Massimo Bernardi, Curator at MUSE and Research associate at Bristol's School of Earth Sciences, said: "We were excited to see that the footprints and skeletons told the same story. We had been studying the footprints in the Dolomites for some time, and it's amazing how clear cut the change from 'no dinosaurs' to 'all dinosaurs' was."

The point of explosion of dinosaurs matches the end of the Carnian Pluvial Episode, a time when climates shuttled from dry to humid and back to dry again.

It was long suspected that this event had caused upheavals among life on land and in the sea, but the details were not clear. Then, in 2015, dating of rock sections and measurement of oxygen and carbon values showed just what had happened.

There were massive eruptions in western Canada, represented today by the great Wrangellia basalts - these drove bursts of global warming, acid rain, and killing on land and in the oceans.

Co-author Piero Gianolla, from the University of Ferrara, added: "We had detected evidence for the climate change in the Dolomites. There were four pulses of warming and climate perturbation, all within a million years or so. This must have led to repeated extinctions."

Professor Mike Benton, also a co-author, from the University of Bristol, said: "The discovery of the existence of a link between the first diversification of dinosaurs and a global mass extinction is important.

"The extinction didn't just clear the way for the age of the dinosaurs, but also for the origins of many modern groups, including lizards, crocodiles, turtles, and mammals - key land animals today."

*Paper: 'Dinosaur diversification linked with the Carnian Pluvial Episode' by M. Bernardi, P. Gianolla, F. Petti, P. Mietto and M. Benton in* Nature Communications *- DOI: 10.1038/s41467-018-03996-1. http://www.nature.com/ncomms*

***http://bit.ly/2F5x7Ly***

## Moss capable of removing arsenic from drinking water discovered

***A moss capable of removing arsenic from contaminated water has been discovered by researchers from Stockholm University.***

And it happens quickly - in just one hour, the arsenic level is so low that the water is no longer harmful for people to drink. The study has been published in the journal Environmental Pollution.

The aquatic moss Warnstofia fluitans, which grows in northern Sweden, has the ability to quickly absorb and adsorb arsenic from water. The discovery allows for an environmentally friendly way to purify water of arsenic. One possible scenario is to grow the moss in streams and other watercourses with high levels of arsenic.

**Water in mining areas often contaminated**

In the northern part of Sweden, water from mining areas is often contaminated by arsenic.

"We hope that the plant-based wetland system that we are developing will solve the arsenic problem in Sweden's northern mining areas," says Maria Greger, associate professor at the Department of Ecology, Environment and Plant Sciences at Stockholm University and leader of the research group.

**High capacity for quick uptake of arsenic**

"Our experiments show that the moss has a very high capacity to remove arsenic. It takes no more than an hour to remove 80 per cent of the arsenic from a container of water. By then, the water has reached such a low level of arsenic that it is no longer harmful to people," says research assistant Arifin Sandhi, who has conducted the experiments.

In 2004, the use of arsenic compounds in wood products was banned, but arsenic still reaches ground and water systems due to mining. This happens because the ground and bedrock in certain parts of Sweden naturally contain arsenic. As a result, the drinking water and water used for the irrigation of crops also contains elevated levels of arsenic. The plants absorb the arsenic from the soil, and it eventually ends up in the food that we eat. In Sweden, this applies to wheat, root vegetables, leafy greens, etc. In other countries, there are high levels in rice, for example.

"How much arsenic we consume ultimately depends on how much of these foods we eat, as well as how and where they were grown. Our aim is that the plant-based wetland system we are developing will filter out the arsenic before the water becomes drinking water and irrigation water. That way, the arsenic will not make it into our food," says Maria Greger.

*The article, Phytofiltration of arsenic by aquatic moss (*Warnstorfia fluitans*), is available to read here: http://www.sciencedirect.com/science/article/pii/S026974911731206X*

http://bit.ly/2HOyIbA

# Fermentation byproduct suppresses seizures in nerve agent poisoning

***Compound formed during fermentation of beer, wine has potential to prevent organophosphate-triggered seizures from developing into epilepsy***

A compound found in trace amounts in alcoholic beverages is more effective at combating seizures in rats exposed to an organophosphate nerve agent than the current recommended treatment, according to new research published in eNeuro.

Left untreated, organophosphate poisoning can lead to severe breathing and heart complications. It is also known to cause seizures. Some patients are resistant to treatment with the anti-anxiety drug diazepam, the first line of defense for such poisoning, and its effectiveness decreases the longer the seizure lasts.

Asheebo Rojas and colleagues compared the ability of two treatments -- diazepam and the anesthetic urethane (ethyl carbamate), commonly formed in trace amounts during fermentation of beer and wine from the reaction of urea and ethanol -- to interrupt seizures in rats exposed to the organophosphate diisopropyl fluorophosphate.

The researchers found urethane to be more effective than diazepam, suppressing seizures for multiple days and accelerating recovery of weight lost while protecting the rats from cell loss in the hippocampus. They did not observe any evidence of lung tumors in the urethane-treated animals seven months later, suggesting that the dose used in this study is not carcinogenic.

The findings point to urethane or a derivative as a potential therapeutic for preventing organophosphate-triggered seizures from developing into epilepsy.

*Article: Beneficial outcome of urethane treatment following status epilepticus in a rat organophosphorus toxicity model*

*DOI: https://doi.org/10.1523/ENEURO.0070-18.2018*

http://bit.ly/2K27RJR

# Ear infections can lead to meningitis, brain abscess and other neurological complications

***Antibiotics have greatly reduced the dangers of ear infections, but serious neurological complications still occur***

MAYWOOD, IL - While antibiotics have greatly reduced the dangers of ear infections, serious neurological complications, including hearing loss, facial paralysis, meningitis and brain abscess still occur, according to a report in the journal *Current Neurology and Neuroscience Reports*.

The article was written by Loyola Medicine otolaryngologists Michael Hutz, MD, Dennis Moore, MD, and Andrew Hotaling, MD.

Otitis media occurs when a cold, allergy or upper respiratory infection leads to the accumulation of pus and mucus behind the eardrum, causing ear ache and swelling. In developed countries, about 90 percent of children have at least one episode before school age, usually between the ages of six months and four years. Today, secondary complications from otitis media occur in approximately 1 out of every 2,000 children in developed countries.

The potential seriousness of otitis media was first reported by the Greek physician Hippocrates in 460 B.C. "Acute pain of the ear with continued high fever is to be dreaded for the patient may become delirious and die," Hippocrates wrote.

The deadliest complication of otitis media is a brain abscess, an accumulation of pus in the brain due to an infection. The most common symptoms are headache, fever, nausea, vomiting, neurologic deficits and altered consciousness. With modern neurosurgical techniques, most brain abscesses can be suctioned or drained, followed by IV antimicrobial treatment for six to eight weeks. During the past 50 years, mortality worldwide from brain abscesses has decreased from 40 percent to 10 percent and the rate of full recovery has increased from 33 percent to 70 percent.

**Other complications include:**

**Bacterial meningitis:** Symptoms include severe headache, high fever, neck stiffness, irritability, altered mental status and malaise. As the infection spreads, the patient develops more severe restlessness, delirium and confusion. Treatment is high-dose IV antibiotics for 7 to 21 days.

**Acute mastoiditis:** This is an infection that affects the mastoid bone located behind the ear. It must be treated to prevent it from progressing to more serious complications. Treatments include IV antibiotics and placement of a drainage tube.

**Hearing loss:** Permanent hearing loss is rare, occurring in about 2 out of every 10,000 children who have otitis media.

Facial paralysis: Prior to antibiotics, this debilitating complication occurred in about 2 out of 100 cases of otitis media. Since antibiotics, the rate has dropped to 1 in 2,000 cases. It should be treated as an emergency. About 95 percent of otitis media patients who develop facial paralysis recover completely.

"Antibiotic therapy has greatly reduced the frequency of complications of otitis media," Drs. Hutz, Moore and Hotaling wrote. "However, it is of vital importance to remain aware of the possible development of neurologic complication. . . . In order to reduce morbidity, early deployment of a multidisciplinary approach with prompt imaging and laboratory studies is imperative to guide appropriate management."

Dr. Hutz is a resident, Dr. Moore is an assistant professor and Dr. Hotaling is a professor emeritus in Loyola Medicine's department of otolaryngology. Their paper is titled, "Neurological Complications of Acute and Chronic Otitis Media."

***http://bit.ly/2qL5yBK***

## Reversing brain injury in newborns and adults

***Discovery of new molecule could lead to more effective treatments for MS, dementia, cerebral palsy***

Children and adults diagnosed with brain conditions such as cerebral palsy, multiple sclerosis and dementia may be one step closer to obtaining new treatments that could help to restore normal function.

Researchers at OHSU in Portland, Oregon, have identified a new molecule within the brain's white matter that blocks the organ's ability to repair itself following injury.

"By preventing the production of this molecule, we can create an effective pathway to allow the brain to continue its regenerative process. This may help to limit long-term physical and mental disability associated with devastating neurological conditions," said Stephen Back, M.D., Ph.D., Clyde and Elda Munson Professor of Pediatric Research and Pediatrics, OHSU School of Medicine, OHSU Doernbecher Children's Hospital.

The results of the study published today in the Journal of Clinical Investigation.

**Discovering the 'bad actor'**

Hyaluronic acid, one of the largest molecules in the human body, fills spaces between cells, lubricates joints and accumulates in lesions -- or abnormalities -- within the brain's white matter. This build-up is known to halt the brain's repair process, also called myelination, causing dramatic disruption to overall brain function.

To better understand the repair roadblocks created by hyaluronic acid, Back and colleagues showed that while brain lesions break down these large molecules into a broad range of sizes, only one specific-sized fragment will selectively block the development of brain cells needed to promote repair.

By tracing the molecular pathway that prevented brain repair, the researchers discovered that the specialized fragment also activated a protein called FoxO3, which blocked key genes that turn on the repair process. Remarkably, this road block did not allow other strong repair signals to detour around it.

"We've identified a molecule that plays the role of the 'bad actor.' In essence, it hijacked the molecular machinery of the immune system and repurposed it to shut down brain repair after injury," said Back. "And, while this new molecule may not be easily detected in the brain, FoxO3 may serve as a viable biomarker for identifying its detrimental effects

in the white matter, creating an opportunity for further research and targeted therapies to fully reverse the impacts of brain injury for people of all ages."

**What's next?**

"For many years, researchers and clinicians alike have struggled to understand and effectively treat the significant physical disabilities associated with white matter injury," said study co-author Larry Sherman, Ph.D., professor, Division of Neuroscience, Oregon National Primate Research Center; and professor of cell, developmental and cancer biology, OHSU School of Medicine. "This discovery means that we now have the potential to start looking at multiple ways of intervening to promote brain repair that weren't available to use before."

One promising direction is the development of new pharmaceuticals that can prevent the generation of hyaluronic acid fragments. Additionally, says Back, new understanding of the brain's pathway to repair may provide health care professionals with new insights that will positively impact therapies such as stem cell transplantation.

*This study was conducted in collaboration with University of Nebraska-Lincoln, the University of Oklahoma Health Sciences Center and the Oregon National Primate Research Center at OHSU. Taasin Srivastava, Ph.D., a post-doctoral researcher in the OHSU School of Medicine is the study's lead author.*

***http://bit.ly/2K2x72s***

## Can an Opioid Overdose Drug Help Stroke Patients Recover?

***The same medication used to save lives by reversing opioid overdoses may also benefit nonopioid users.***

**By Cari Nierenberg, Live Science Contributor**

In a new study done in rats, the medicine, called naloxone, was shown to help the brain to recover from a stroke.

Researchers found that when male rats were treated for one week with naloxone after having an ischemic stroke, they had an improved recovery, compared with rats who did not receive naloxone. (An ischemic stroke occurs when blood flow to the brain is interrupted, usually because of a blood clot, which deprives the brain of oxygen and damages nerve cells in the area.)

Because the study was done in rats, more research is needed to confirm the findings in people. However, naloxone might play a role in stroke recovery because the drug has anti-inflammatory properties and can reduce the activity of the microglia, which are the primary immune cells of the brain, according to the study findings, published today (April 16) in the journal eNeuro.


***Naloxone is used to treat opioid overdoses.*** **Andrew Burton/Getty Images**

Previous research has shown that naloxone affects the microglia, which are very active contributors to the inflammation that occurs in the brain following a stroke, said study co-author Brandon Harvey, a researcher at the National Institute on Drug Abuse in Baltimore. So, in this study, the researchers wanted to see whether giving naloxone after a stroke could decrease the activity of the brain's immune cells and reduce the associated inflammation, leading to improved recovery from the stroke, he said.

**Improved stroke recovery**

In the new study, the researchers gave 65 male rats naloxone twice a day through the nose at a dose considered to be safe in humans. (Naloxone is often given as a nasal spray to reverse an overdose, according to the study.) The study showed that the drug was most effective when treatment was started within 16 to 36 hours after a stroke and lasted for seven days.

The findings showed that when naloxone was given after a stroke, during a period when immune-cell activity in the brain was peaking, it had beneficial effects on recovery, said study co-author Mikko Airavaara, principal investigator at the Institute of Biotechnology at the University of Helsinki in Finland. (Immune cells in the rats' brains were

active as early as two days after a stroke and reached their peak activity seven days after a stroke, according to the findings.)

Airavaara said that naloxone works reducing inflammation in the brain and reducing the loss of nerve cells, which can improve the brain's ability to recover after a stroke.

These findings are important because there is no drug treatment now that helps the brain recover after a stroke, Airavaara told Live Science. So, developing a drug therapy that could promote recovery for the 10 million people worldwide who have strokes each year would be groundbreaking, he said.

Indeed, because naloxone has been used to treat opioid overdoses for nearly 50 years, the idea of repurposing the drug for stroke is intriguing, Harvey said.

**What about people?**

Still, more research is needed in animals before naloxone is studied in people who have had a stroke.

It would be important to establish that the drug's beneficial effects would work not only in male rats but in female rats as well, Harvey told Live Science.

The current study was able to establish an effective delivery method for the drug — through the nose, which is one of the methods already used to reverse opioid overdose — and a suggested dosing pattern (when to give the drug) to possibly translate these findings into clinical practice in the future, Harvey said.

Daniel Lackland, a professor of epidemiology in the neurology department at the Medical University of South Carolina in Charleston, who was not involved in the new research, said that there is a need to identify other treatments for stroke recovery. Currently, rehabilitation includes physical-, occupational- and speech-therapy programs; however, treatments that target physiological changes in the brain are lacking, he said.

In addition, recovering from a stroke has not had the same success rates as recovering from heart disease, said Lackland, who is a spokesperson for the American Stroke Association.

This study explored the possibility that a new drug may contribute to stroke recovery, and this drug appears to have some benefits in animals, Lackland told Live Science. Though the findings need to be replicated in additional animal studies, these results give hope for the future of possible trials in humans, he said.

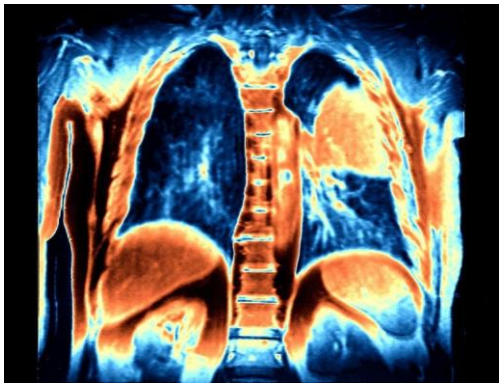
***https://nyti.ms/2qQYWlA***

## Lung Cancer Patients Live Longer With Immune Therapy

***Odds of survival can greatly improve for people with the most common type of lung cancer if they are given a new drug that activates the immune system along with chemotherapy, a major new study has shown.***

**By DENISE GRADY APRIL 16, 2018**

The findings, medical experts say, should change the way doctors treat lung cancer: Patients with this form of the disease should receive immunotherapy as early as possible.



***A colored magnetic resonance imaging scan of a cancerous tumor in the lung, in orange, upper right. A study suggests "that chemotherapy alone is no longer a standard of care," its lead author said.*** **Zephyr/Science Source**

"What it suggests is that chemotherapy alone is no longer a standard of care," said Dr. Leena Gandhi, a leader of the study and director of the Thoracic Medical Oncology Program at the Perlmutter Cancer Center at New York University Langone Health.

Immunotherapy has been making steady gains against a number of cancers. Four such drugs, called checkpoint inhibitors, which unleash

the patient's own immune system to kill malignant cells, have been approved so far.

They cost more than $100,000 a year, can have serious side effects and help only some patients, generally fewer than half. But when the drugs work, responses can be long-lasting, and researchers are rushing to find ways to combine treatments to improve their effects and to determine which formulation is best for each patient.

"I've been treating lung cancer for 25 years now, and I've never seen such a big paradigm shift as we're seeing with immunotherapy," said Dr. Roy Herbst, Chief of Medical Oncology at the Yale Cancer Center. He was not involved in the pembrolizumab study.

Lung cancer is the leading cause of cancer death globally, causing 1.7 million deaths a year. In the United States, it is expected to kill more than 154,000 people in 2018.

Patients in the study had an advanced stage of non-squamous non-small-cell lung cancer. The immune-activating drug was a checkpoint inhibitor called pembrolizumab, or Keytruda, made by Merck, which paid for the study. The chemotherapy was a drug called pemetrexed, plus either carboplatin or cisplatin.

Dr. Gandhi said chemotherapy alone had only a "modest benefit," and could add only a few months of life, with most patients surviving about a year or less. The combination treatment is a significant improvement, she said. It is already approved as a first-line treatment for this disease, so it should be covered by health insurers.

She was scheduled to present the results on Monday in Chicago at a meeting of the American Association for Cancer Research, and they were also published in The New England Journal of Medicine.

Other studies presented at the meeting also highlighted advances in immunotherapy against lung cancer, but were at earlier points in the research and less likely to bring about immediate changes in medical practice.

"If you want to see long-term survival, you've got to give immunotherapy as soon as possible," Dr. Herbst said. "Chemotherapy has limitations. Immunotherapy has the ability to cure. I lead the Yale lung team. We have patients on these immunotherapies alive more than eight years."

Other studies in lung cancer have involved another checkpoint inhibitor, nivolumab, or Opdivo (made by Bristol-Myers Squibb), which works in a similar way to pembrolizumab. The data are not conclusive, but Dr. Herbst said, "In lung cancer, my suspicion is these drugs are the same, like Coke vs. Pepsi."

Most patients stay on the drugs for two years, he said. One Yale patient who has survived for eight years took the drug for two years and has remained well ever since. Another had to stop because of side effects after two or three months, but is well two years later.

Dr. Herbst offered several theories about why chemotherapy and immunotherapy could work well together. He said that tumor cells were like bags of hidden proteins that, if exposed, the immune system could use as targets to find and attack cancer. By killing some tumor cells, chemotherapy could pop open the bags, release the contents and help immune cells — unleashed by the checkpoint drugs — to identify their prey. It is also possible, he said, that chemotherapy may kill some immune cells that interfere with the cancer-killing action of other parts of the immune system.

Dr. Gandhi's study included 616 patients with advanced lung cancer, ages 34 to 84, from medical centers in 16 countries. Their tumors lacked certain mutations that would have made them eligible for other, so-called "targeted" treatments. They were picked at random to receive either chemotherapy plus immunotherapy, or chemotherapy plus a placebo, with two thirds receiving the combination that included immunotherapy.

After a median follow-up of 10.5 months, those in the immunotherapy group were half as likely to die. The median overall survival was 11.3 months in those who did not receive immunotherapy, whereas survival in the immunotherapy group was longer and the median has not yet been reached.

But patients in the immunotherapy group had more kidney problems, more immune-related adverse events and were more likely to stop treatment because of side effects.

The estimated survival at 12 months was 69.2 percent in the group that received immunotherapy, and 49.4 percent in those who did not.

"I think we were all surprised at the magnitude of benefit and how clear the difference was at an early analysis, and that we could tell there was an overall survival difference," Dr. Gandhi said, adding that there was "a lot of excitement" at the conference about her study and several others involving immunotherapy.

"It represents a sea change in the way we think about treating lung cancer," she said. "All of it is better than what we've been using for years. Going forward, it will only get better."

Patients were tested for a biomarker used to predict whether pembrolizumab is likely to help them. The drug alone is already approved to treat patients with high levels of those markers. But this study included patients with varying levels. Those with high levels of the marker fared somewhat better with immunotherapy than those with low levels — but even those with low levels were helped.

"The data are impressive," Dr. Herbst said. "We're making progress, but still only benefiting 30 to 40 percent of patients. There's a lot more room to do better. We have to keep looking for new things and new approaches."

***http://bit.ly/2vwqwRr***

## "Nuclear geyser" may be origin of life

***The perfect for conditions for life – including a handy power source – may have been a natural nuclear reactor on the early Earth.***

**Richard A. Lovett reports.**

Life may not have originated in the primordial soup of an ancient pond, according to scientists, but rather in a "nuclear geyser" powered by an ancient uranium deposit.

Shigenori Maruyama of Tokyo Institute of Technology says the idea came from what chemists know about crucial compounds in our own bodies. Many of these compounds – including DNA and proteins - are polymers formed from chains of smaller building blocks.

Each of these molecules serves a different purpose in the body, but something they all have in common, says Nicholas Hud, a chemist from Georgia Institute of Technology, Atlanta, is that a molecule of water is released when each new building block is added.

"There is a theme here," he said last week at a NASA-sponsored symposium on the early solar system and the origins of life. To a chemist, this suggests that these biopolymers must have originated under relatively dry conditions.

Otherwise, Hud says, the presence of water would have forced the reactions to run backwards, breaking chains apart. But, there's a problem: most scientists assume life started in water.

The solution to this paradox, according to Hud, comes from realizing that water comes and goes. The major chemicals of life, and presumably life itself, may have formed in an environment that was alternately wet and dry. "It could be seasonal," he says. "It could be tides. It could be aerosols that go up [into the air] and come back down."

Some prebiotic chemical reactions occur easily at moderate temperatures, but others, says Robert Pascal, a physical organic chemist from the University of Montpellier, France, require a more concentrated source of energy. This energy may have come from the sun, which in the early solar system was considerably more active than today. But another source is radiation. Which brings us back to nuclear geysers.

Based on analyses similar to Hud's and Pascal's, Maruyama has identified nine requirements for the birthplace of life. One place where all can occur at once, Maruyama says, is in the plumbing of a nuclear geyser.

This would not only produce heat to power the geyser, but produce radiation strong enough to break the recalcitrant molecular bonds of water, nitrogen, and carbon dioxide, all of which must be cleaved in order to produce critical prebiotic compounds. Periodic eruptions of the geyser would also produce alternating wet and dry cycles, and water

draining from the surface would bring back dissolved gases from the atmosphere. The rocks lining the geyser's subterranean channels would provide a source of minerals such as potassium and calcium.

"This is the place I recommend [for the origin of life]," Maruyama says. Once life originated, he says, it would have been spewed onto the surface and from there into the oceans. From there, it spread to every known habitable niche on the modern Earth.

Extraterrestrial life (or at least life as we know it), he says, would need similar conditions in which to originate.

That, he thinks, means the best place to look for it in our solar system is Mars. However habitable the subsurface oceans of outer moons such as Ganymede, Europa, and Titan may be for bacteria, they likely lack the conditions needed for the origin of life as we know it, he says.

As for exoplanets? Similar conditions are also needed there, he says, including not only an energy source to power pre-biotic reactions, but a "triple junction" between rock, air, and water, where all the needed materials can come together simultaneously.

***https://nyti.ms/2Jh98eT***

## Diamonds in a Meteorite May Be a Lost Planet's Fragments

***Diamonds inside a meteorite may come from a destroyed planet that orbited our sun billions of years ago***

**By NICHOLAS ST. FLEUR APRIL 18, 2018**

In 2008, chunks of space rock crashed in the deserts of Sudan. Diamonds discovered inside one of the recovered meteorites may have come from a destroyed planet that orbited our sun billions of years ago, scientists said on Tuesday. If confirmed, they say, it would be the first time anyone has recovered fragments from one of our solar system's so-called "lost" planets.

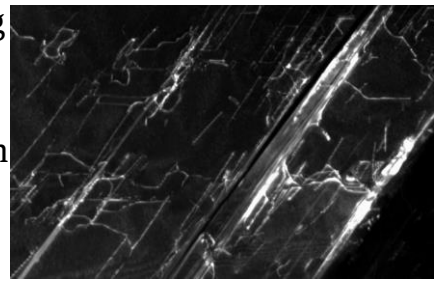
"We have in our hands a piece of a former planet that was spinning around the sun before the end of the formation of today's solar system," said Philippe Gillet, a planetary scientist at the Federal Institute of Technology in Lausanne, Switzerland and an author of the paper that was published in Nature Communications.

Dr. Gillet's colleague Farhang Nabiei made the discovery while taking high-resolution images of a meteorite that had landed in the Nubian Desert in Sudan about a decade ago. The space rock is classified as ureilite, a type of rare meteorite that has embedded within it several different types of minerals.

***Fragments of the 2008 TC3, or Almahata Sitta, meteorite that fell to Earth in 2008. The diamonds discovered inside one of the fragment may have come from a protoplanet that orbited the sun billions of years ago.*** **Peter Jenniskens/SETI/NASA**

And inside this one, they found diamonds.

The nano-sized gems were much larger than any meteorite diamond that had been previously found, according to Dr. Gillet. Upon further inspection the team noticed that the diamonds were far from crystal clear. They were riddled with tiny imperfections, called inclusions, made of chromite, phosphate and iron-nickel sulfides.



***A transmission electron microscopy image of one of the diamonds recovered from the meteorite.*** **Credit Dr. F. Nabiei/Dr. E. Oveisi, EPFL, Switzerland**

Those flaws made the diamond extraordinary.

"What for a jeweler is an imperfection becomes for me something that is very useful because it tells me about the history of the diamond," said Dr. Gillet. "It has a chemistry which has no equivalent in the solar system today, in terms of planets," he said.

Our solar system was born of chaos. Some 4.5 billion years ago, prevailing theories hold that dozens of chunks of rock and dust, called protoplanets, circled our sun and collided with each other like cosmic

billiard balls. Eventually, the collisions forged the rocky planets that we know today — Mercury, Venus, Mars and, of course, Earth. Our moon is thought by some scientists to have formed from debris spewed by such an impact between Earth and a protoplanet called Theia.

The inclusions in the meteorite's diamonds told of a similarly turbulent past. Because of the diamonds' size and chemistry, Dr. Gillet and his team concluded that the diamonds formed under intense pressure, of about 20 giga-pascals, which is close to the pressure seen 400 miles below Earth's surface where the upper mantle transitions into the lower mantle.

Pressure that high could have been reached only inside a planetary body that was between the sizes of Mercury and Mars, he said.

And because the chemistry of the inclusions did not match what is known on planets in today's solar system, they think the diamonds came from a protoplanet that existed between 4.54 and 4.57 billion years ago. That protoplanet most likely collided with another planet and expelled debris that ended up in the asteroid belt, where it wandered for billions of years before plunging to Earth.

Adrian Brearley, an earth scientist at the University of New Mexico who was not involved in the study, said the findings were compelling. "The authors tie their electron microscope observations together with experimental studies to provide very sound arguments for a large planetary body for the ureilites," he said.

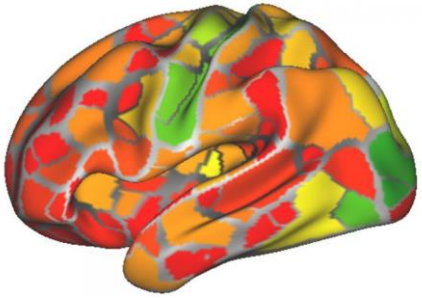
***http://bit.ly/2qUMmSu***

## Brain scans may help diagnose neurological, psychiatric disorders

***Study shows that brain networks reliably track individuals over time***

There are no laboratory tests to diagnose migraines, depression, bipolar disorder and many other ailments of the brain. Doctors typically gauge such illnesses based on self-reported symptoms and behavior.

Now, a new study shows that a kind of brain scan called functional connectivity MRI (fcMRI) - which shows how brain regions interact - can reliably detect fundamental differences in how individual brains are wired. As such, the technique potentially could be used to distinguish healthy people from people with brain diseases or disorders, and provide insight into variations in cognitive ability and personality traits. The findings are published April 18 in Neuron.



***Brain networks from nine people were analyzed to generate the heat map above, which shows the areas that change the most (red) to the least (green), from person to person. A new study shows that individual brain networks are remarkably stable from day to day and while undertaking different tasks, suggesting that finding differences between individuals could help diagnose brain disorders or diseases.*** **Credit: Caterina Gratton**

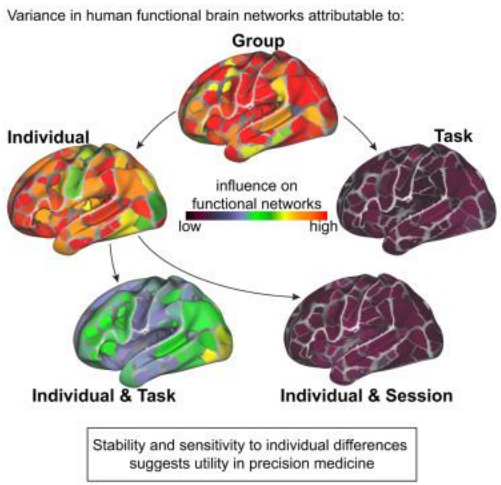
"This is a step toward realizing the clinical promise of functional connectivity MRI," said senior author Steven Petersen, PhD, the James S. McDonnell Professor of Cognitive Neuroscience in Neurology and a professor of neurosurgery, of biomedical engineering, of psychological and brain sciences, and of radiology. "Before we can develop diagnostic tests based on fcMRI, we need to know what it is actually measuring. We show here that it's not measuring what you're thinking, but how your brain is organized. That opens the door to an entire new field of clinical testing."

Petersen, postdoctoral researcher and first author Caterina Gratton, PhD, and colleagues analyzed a set of data collected by the Midnight Scan Club, a group of Washington University scientists who took turns undergoing myriad scans in an MRI machine late at night, when the demand for such machines and, consequently, the usage fees tend to be low.

The researchers analyzed data from more than 10 hours of fcMRI scans on each of nine people, collected in 10 separate one-hour sessions for each person. During the scans, each person performed tasks related to vision, memory, reading or motor skills, or rested quietly.

Functional MRI scans generate a dynamic map of the outer surface of the brain, showing changing hot spots of activity over time. To create

a functional connectivity map, Gratton divided the brain's surface into 333 regions and identified areas that became active and inactive in unison. She then constructed brain network maps for each individual, showing patterns of correlation between parts of the brain.




The sheer quantity of data available on each person allowed her to analyze how much an individual's brain networks changed from day to day and with different mental tasks. The answer? Not much.

"Brain networks captured by fcMRI are really about the individual," Gratton said. "Whether someone's watching a movie or thinking about her breakfast or moving her hands makes only a small difference. You can still identify that individual by her brain networks with a glance."

The consistency of the fcMRI scans makes them a promising diagnostic tool. Although the technique's potential to identify brain disorders and diseases was noted years ago, fcMRI-based diagnostic tests have yet to make their way into doctors' offices. Progress has been stymied by confusion over whether the scans reflect fundamental, stable features of the brain, or if they change with every passing thought.

Further, the researchers found that the technique was powerful enough to distinguish people who were extraordinarily alike. All of the scanned brains belonged to young, healthy scientists and doctors.

"We need more data before we can know what is normal variation in the population at large," Gratton said. "But the individual differences were really easy to pick up, even in a population that is really very similar. It's exciting to think that these individual differences may be related to personality, cognitive ability, or psychiatric or neurological disease. Thanks to this work, we know we have a reliable tool to study these possibilities."

http://bit.ly/2HmmkOK

## Russia appears to have surrendered to SpaceX in the global launch market

***"The 4 percent stake isn't worth the effort to try to elbow Musk and China aside."***

**Eric Berger - 4/18/2018, 11:01 PM**

As recently as 2013, Russia controlled about half of the global commercial launch industry with its fleet of rockets, including the Proton boosters. But technical problems with the Proton, as well as competition from SpaceX and other players, has substantially eroded the Russian share. This year, it may only have about 10 percent of the commercial satellite launch market, compared to as much as 50 percent for SpaceX.

In the past, Russian space officials have talked tough about competing with SpaceX in providing low-cost, reliable service to low-Earth and geostationary orbit. For example, the Russian rocket corporation, Energia, has fast-tracked development of a new medium-class launch vehicle that it is calling Soyuz-5 to challenge SpaceX.

On Tuesday, however, Russia's chief spaceflight official, Deputy Prime Minister Dmitry Rogozin, made a remarkable comment about that country's competition with SpaceX.

"The share of launch vehicles is as small as 4 percent of the overall market of space services," Rogozin said in an interview with a Russian television station. "The 4 percent stake isn't worth the effort to try to elbow Musk and China aside. Payloads manufacturing is where good money can be made."

According to an independent analysis, the global launch market is worth about $5.5 billion annually. Losing its half-share of this market, therefore, has probably cost the Russians about $2 billion, which is a significant fraction of its non-military aerospace budget.

Rogozin is correct that satellite manufacturing is a considerably larger industry, worth about $14 billion a year. But like launch, this is also a competitive industry, and Russia has historically not had a dominant

position in the satellite manufacturing and services industry like it has had in launch. It was the Soviet Union that first launched a satellite, Sputnik, and then a human, Yuri Gagarin, into space, after all.

What seems most remarkable about Rogozin's comment is that, for the first time publicly, the world's most storied launch provider appears to be ceding the commercial launch market to other providers—most notably a rocket company that didn't exist until 2002, and flew its first orbital rocket less than a decade ago.

***http://bit.ly/2F6a57f***

## Tiny Shrimp Mix Up the Ocean

***Crowds of zooplankton swimming upward generate large downward jets of water, a study finds.***

**By Catherine Offord | April 18, 2018**

Tiny shrimp and other zooplankton swimming in the ocean could play a major role in ocean mixing, according to researchers at Stanford University. The team reports that as large numbers of the creatures swim upward towards light during the day, they generate downward jets—a finding that suggests the animals could have substantial effects on the structure and composition of the world's oceans. The results were published today (April 18) in *Nature*.

"Whether or not swarming adds up to genuine mixing has been the big question in this business for the past decade or so," Nicholas Butterfield, a paleobiologist at the University of Cambridge who was not involved with the work, tells *Science*. "This study makes a pretty good claim for nailing it."

To simulate a tiny piece of the ocean in the lab, Stanford biophysicist John Dabiri and colleagues set up two large tanks of water, and added more than 100,000 brine shrimp, *Artemia salina*, to each. Then, they encouraged the shrimp to swim upward with lights, and visualized the effects using several imaging techniques.

The team found that even when the water in the tanks was stratified—that is, it contained distinct sections differing in salinity and therefore density—the collective movement of many shrimp swimming upward resulted in large, downward jets of water.

The movement has yet to be observed in the open ocean, the authors note in their paper. However, "the results illustrate the potential for marine zooplankton to considerably alter the physical and biogeochemical structure of the water column," the authors write, "with potentially widespread effects owing to their high abundance in climatically important regions of the ocean."

***https://bbc.in/2qKvRZR***

## Keeping livers 'alive' boosts transplant success, trial finds

***Keeping donated livers "alive" with a machine prior to transplants boosts the chances of a successful operation, a landmark trial has found.***

**By Alex Therrien Health reporter, BBC News**

Usually livers are kept in ice prior before the surgery, but many become damaged and unusable as a result. For this study, scientists put them in a perfusion machine, pumping the organs with blood, nutrients and medicines. More of these "warm" livers went on to be transplanted and showed less damage than the "cold" ones, the trial found.

Scientists said the study could help to reduce the significant proportion of people who die waiting for a new liver and potentially "transform" how organ transplants are carried out.

**'Major impact'**

The randomised controlled trial involved 222 liver transplants in seven European centres. It compared liver transplants where the organs were first preserved in an ice box with those kept "alive" outside the body using a so-called normothermic perfusion machine.

Out of the 220 transplants scientists analysed, the study found there was 50% less tissue damage in the "warm" livers - a key marker of how likely the organ is to survive as well as the transplant patient themselves.

Scientists were also able to successfully transplant more of the warm livers than cold ones. Just 16 out of 137 warm livers needed to be discarded compared with 32 out of 133 cold ones, meaning 222

transplants were able to go ahead. All but two were analysed by the team.

Prof Peter Friend, one of the authors of the study in the journal Nature and one of the inventors of the machine, said currently about a third of donated livers could not be used for transplantation due to a range of factors.

These include livers taken from elderly people or those in poor health, which were more likely to fail, damage occurring while the organ was removed from the donor's body and damage sustained while being kept in ice.

About 20% of patients die while waiting for a liver transplant, he said.

Keeping the liver "alive" outside the body helps it recover from the damage it suffers during the process of being removed from the donor's body, authors said. "There's a huge issue in terms of the [high] number of patients compared to donor organs, and yet we're not using all of the donor organs that are available," Prof Friend told the BBC. "If we can go some way towards utilising the livers that are not transplanted it would have a major impact."

**Analysis - BBC medical correspondent Fergus Walsh**

***There are machines that can keep the heart beating and nourished outside the body.***

***I have witnessed one of these heart-in-a-box machines in operation - and could see - and even touch - a pig's heart beating under the plastic covers.***

***There are also machines that can keep kidneys preserved at body temperature.***

***There has been such significant progress in this field that this trial may signal the beginning of the end of keeping donor organs on ice - although it could be several years before every transplant centre has this technology.***

**'I feel a lot fitter'**

David Radford, 63, from Oxford, needed a transplant after having liver cancer. He took part in the trial and was one of those who received a "warmed" liver.

Mr Radford said his surgeon told him that when he performed the transplant "he had never seen anything quite like it before".

"Normally when he inserted an organ into the recipient it took about 30 seconds or so before it started working and there was a major dip in the blood pressure," Mr Radford said. "But with me he was quite surprised that there was no change in the blood pressure at all and everything seemed to start working immediately."

Mr Radford has since been skiing and now regularly does classes of tai-chi, yoga and kung-fu. "It hasn't impaired me at all. If anything I feel a lot fitter than before."

**'Landmark study'**

Much smaller studies have looked at the use of the technology before but this is the first large randomised controlled trial to compare it with ice-box storage to see which is most effective.

Prof Friend said he thought the technology could potentially transform how organ transplants are carried out.

"The concept of keeping organs alive and functioning appears to be completely transferrable between different other organ types," he said.

Liver perfusion is currently performed on the NHS in a small number of specialist centres in the UK.

But experts say the technology is expensive and a cost analysis will need to be carried out before it is offered more widely.

Stephen Wigmore, professor of transplant surgery at the University of Edinburgh, who was not involved in the trial, said it was a "landmark" study. "Whereas before the conclusions that could be drawn [about organ perfusion] were slightly weak and anecdotal, this is scientifically robust in its design and statistical power, so we're more certain about the outcomes being good in this study."

Barry Fuller, professor of surgery at University College London, said the research presented a "very significant advance" in the use of the technology. "The challenge now is to make the technology widely used and logistically manageable and affordable."

http://bit.ly/2HhE2ae

## Dogs could be more similar to humans than we thought

***Dog and human gut microbiomes have more similar genes and responses to diet than we previously thought, according to a study published in the open access journal, Microbiome.***

Dr Luis Pedro Coelho and colleagues from the European Molecular Biology Laboratory, in collaboration with Nestlé Research, evaluated the gut microbiome of two dog breeds and found that the gene content of the dogs microbiome showed many similarities to the human gut microbiome, and was more similar to humans than the microbiome of pigs or mice.

Dr Luis Pedro Coelho, corresponding author of the study, commented: "We found many similarities between the gene content of the human and dog gut microbiomes. The results of this comparison suggest that we are more similar to man's best friend than we originally thought."

The researchers found that changes in the amount of protein and carbohydrates in the diet had a similar effect on the microbiota of dogs and humans, independent of the dog's breed or sex. The microbiomes of overweight or obese dogs were found to be more responsive to a high protein diet compared to microbiomes of lean dogs; this is consistent with the idea that healthy microbiomes are more resilient.

Dr Luis Pedro Coelho, commented:

"These findings suggest that dogs could be a better model for nutrition studies than pigs or mice and we could potentially use data from dogs to study the impact of diet on gut microbiota in humans, and humans could be a good model to study the nutrition of dogs.

"Many people who have pets consider them as part of the family and like humans, dogs have a growing obesity problem. Therefore, it is important to study the implications of different diets."

The researchers investigated how diet interacted with the dog gut microbiome with a randomized controlled trial using a sample of 64 dogs, half of which were beagles and half were retrievers, with equal numbers of lean and overweight dogs. The dogs were all fed the same base diet of commercially available dog food for four weeks then they were randomized into two groups; one group consumed a high protein, low carb diet and the other group consumed a high carb, low protein diet for four weeks. A total of 129 dog stool samples were collected at four and eight weeks. The researchers then extracted DNA from these samples to create the dog gut microbiome gene catalogue containing 1,247,405 genes. The dog gut gene catalogue was compared to existing gut microbiome gene catalogues from humans, mice and pigs to assess the similarities in gene content and how the gut microbiome responds to changes in diet.

The authors caution that while humans and dogs host very similar microbes, they are not exactly the same microbes, but very closely related strains of the same species.

***More information:*** *Luis Pedro Coelho et al. Similarity of the dog and human gut microbiomes in gene content and response to diet, Microbiome (2018). DOI: 10.1186/s40168-018-0450-3*

http://bit.ly/2qRwYpX

## NYC Mice Are Packed with Pathogens

***Mice trapped in New York City apartment buildings harbored disease-causing bacteria and antibiotic resistance genes.***

**Christopher Intagliata reports.**

Download MP3

Rats. They're a defining feature of life in New York City, rustling in trash bags, scurrying along the subway tracks—and becoming famous for occasionally eating pizza. But these urban vermin may be less of a threat to human health than their smaller, cuter cousins—the city's mice.

"They're in your buildings, and they get into your kitchen cupboards, and they get behind refrigerators. So they have a real potential to contaminate the environment that you actually live in."

Simon Williams is a microbiologist at Columbia University and the University of Western Australia. He and his colleagues trapped more than 400 mice in apartment building basements in Manhattan, Queens, Brooklyn and the Bronx. They took swabs of the mice's rear ends,

gathered feces from the traps, and subjected both to a battery of genetic tests.

The mice harbored an array of disease-causing bacteria, like shigella, *Clostridium difficile*, salmonella. They also carried a suite of antibiotic-resistance genes, and viruses associated with insects, dogs, chickens and pigs. Mice from a Chelsea apartment building had the most pig virus—perhaps, the scientists say, because they live near the Meatpacking District, which used to have pork processing facilities before fashionable nightclubs took over.

The details are in the journal *mBio*. [Simon H. Williams et al., Viral Diversity of House Mice in New York City; and Simon H. Williams et al., New York City House Mice (*Mus musculus*) as Potential Reservoirs for Pathogenic Bacteria and Antimicrobial Resistance Determinants]

The mere fact that these microbes can be found in poop, though, isn't cause for immediate alarm. "You know we're not saying these bugs are all out to get us. We're just finding the genetic footprint. They're indicators, but we're not saying they're necessarily out there and there's a huge problem. So keep calm, in terms of the public health response."

Further work might tease out whether there's transmission of bacteria between mice feces and humans. Until then, there are plenty of other New Yorkers to investigate.

"Cockroach would be an amazing one to go onto next. I think they have real potential."

***http://bit.ly/2HItAIj***

## Skin cancers linked with reduced risk of Alzheimer's disease

***Decreased risk of Alzheimer's disease associated with malignant melanoma***

Previous studies have demonstrated a decreased risk of Alzheimer's disease (AD) in individuals with various cancers, including non-melanoma skin cancers (including squamous cell cancers and basal cell cancers). A new *Journal of the European Academy of Dermatology & Venereology* study finds that this inverse relationship also holds true for malignant melanoma.

The study included patients aged 60-88 years with a clinic follow-up of at least 1 year and no diagnosis of AD or skin cancer at the beginning of the study. Of 1147 patients who were later diagnosed with malignant melanoma, 5 were diagnosed with subsequent AD. Of 2506 who were diagnosed with basal cell cancer, 5 had a subsequent AD diagnosis, and of 967 who were diagnosed with squamous cell cancer, only 1 had a subsequent AD diagnosis.

After adjustments, a diagnosis of malignant melanoma was associated with a 61% reduced risk of developing AD. For basal cell and squamous cell carcinomas, the reduced risks were 82% and 92%, respectively.

***http://bit.ly/2K3Nqoe***

## Unprecedented wave of large-mammal extinctions linked to ancient humans

***Massive mammals were far more likely than their smaller counterparts to go extinct in regions occupied by ancient humans***

Homo sapiens, Neanderthals and other recent human relatives may have begun hunting large mammal species down to size - by way of extinction - at least 90,000 years earlier than previously thought, says a new study published in the journal Science.

Elephant-dwarfing wooly mammoths, elephant-sized ground sloths and various saber-toothed cats highlighted the array of massive mammals roaming Earth between 2.6 million and 12,000 years ago.

Prior research suggested that such large mammals began disappearing faster than their smaller counterparts - a phenomenon known as size-biased extinction - in Australia around 35,000 years ago.

With the help of emerging data from older fossil and rock records, the new study estimated that this size-biased extinction started at least 125,000 years ago in Africa.

By that point, the average African mammal was already 50 percent smaller than those on other continents, the study reported, despite the fact that larger landmasses can typically support larger mammals.

But as humans migrated out of Africa, other size-biased extinctions began occurring in regions and on timelines that coincide with known human migration patterns, the researchers found.

Over time, the average body size of mammals on those other continents approached and then fell well below Africa's.

Mammals that survived during the span were generally far smaller than those that went extinct.

The magnitude and scale of the recent size-biased extinction surpassed any other recorded during the last 66 million years, according to the study, which was led by the University of New Mexico's Felisa Smith.

"It wasn't until human impacts started becoming a factor that large body sizes made mammals more vulnerable to extinction," said the University of Nebraska-Lincoln's Kate Lyons, who authored the study with Smith and colleagues from Stanford University and the University of California, San Diego.

"The anthropological record indicates that Homo sapiens are identified as a species around 200,000 years ago, so this occurred not very long after the birth of us as a species. It just seems to be something that we do.

"From a life-history standpoint, it makes some sense. If you kill a rabbit, you're going to feed your family for a night. If you can kill a large mammal, you're going to feed your village."

By contrast, the research team found little support for the idea that climate change drove size-biased extinctions during the last 66 million years.

Large and small mammals seemed equally vulnerable to temperature shifts throughout that span, the authors reported.

"If climate were causing this, we would expect to see these extinction events either sometimes (diverging from) human migration across the globe or always lining up with clear climate events in the record," said Lyons, assistant professor of biology at Nebraska.

"And they don't do either of those things."

**Off The Face Of The Earth**

The team also looked ahead to examine how potential mammal extinctions could affect the world's biodiversity. To do so, it posed a question: What would happen if the mammals currently listed as vulnerable or endangered were to go extinct within the next 200 years?

In that scenario, Lyons said, the largest remaining mammal would be the domestic cow. The average body mass would plummet to less than six pounds - roughly the size of a Yorkshire terrier.

"If this trend continues, and all the currently threatened (mammals) are lost, then energy flow and taxonomic composition will be entirely restructured," said Smith, professor of biology at New Mexico. "In fact, mammalian body size around the globe will revert to what the world looked like 40 million years ago."

Lyons said that restructuring could have "profound implications" for the world's ecosystems.

Large mammals tend to be herbivores, devouring large quantities of vegetation and effectively transporting the associated nutrients around an ecosystem. If they continue to disappear, she said, the remaining mammals would prove poor stand-ins for important ecological roles.

"The kinds of ecosystem services that are provided by large mammals are very different than what you get from small mammals," Lyons said. "Ecosystems are going to be very, very different in the future. The last time mammal communities looked like that and had a mean body size that small was after the extinction of the dinosaurs.

"What we're doing is potentially erasing 40 to 45 million years of mammal body-size evolution in a very short period of time."

Smith and Lyons authored the study with Jon Payne of Stanford University and Rosemary Elliott Smith from the University of California, San Diego.

The team received support from the National Science Foundation.

http://bit.ly/2JepBQK

# Study predicts 2018 flu vaccine will have 20 percent efficacy

## *Rice U. study finds egg adaptations will limit efficacy of new flu vaccine*

A Rice University study predicts that this fall's flu vaccine -- a new H3N2 formulation for the first time since 2015 -- will likely have the same reduced efficacy against the dominant circulating strain of influenza A as the vaccine given in 2016 and 2017 due to viral mutations related to vaccine production in eggs.

The Rice method, known as pEpitope (pronounced PEE-epih-tope), was invented more than 10 years ago as a fast, inexpensive way of gauging the effectiveness of proposed flu vaccine formulations. The latest pEpitope study, which is available online this week in *Clinical Infectious Diseases*, suggests pEpitope is a more accurate predictor of vaccine efficacy than long-relied-upon ferret tests, particularly for data gathered in the past decade. The pEpitope method accounts for 77 percent of what impacts efficacy of the vaccine in humans.

pEpitope is a computational method that measures critical differences in the genetic sequences of flu strains. In the new study, the method accurately predicted vaccine efficacy rates for more than 40 years of flu records. These included the past two flu seasons in which vaccines offered only limited protection against the most widely circulating strain of influenza A.

"The vaccine has been changed for 2018-19, but unfortunately it still contains two critical mutations that arise from the egg-based vaccine production process," said Michael Deem, Rice's John W. Cox Professor in Biochemical and Genetic Engineering and professor of physics and astronomy. "Our study found that these same mutations halved the efficacy of flu vaccines in the past two seasons, and we expect they will lower the efficacy of the next vaccine in a similar manner."

Full efficacy data for the 2017-2018 flu season are still being compiled, but pEpitope has predicted it will be around 19 percent against H3N2, the type of influenza A that infected most people in the U.S. in each of the past two years. The Food and Drug Administration chose the same vaccine formulation in 2017 and 2016, in part because the dominant circulating strain stayed the same. In 2016, the vaccine had an efficacy of 20 percent, almost identical to the efficacy of 19 percent predicted by pEpitope.

Efficacy is the measure of how effective a vaccine is at protecting the overall population. A 20 percent efficacy means that in a population, 20 percent fewer vaccinated people will get the flu compared to the unvaccinated people.

Annual flu vaccines are formulated to protect against one type of influenza B and two strains of influenza A, one H3N2 strain and one H1N1 strain. The H and N refer to hemagglutinin and neuraminidase, two proteins that cover the outside of invading flu particles that can cause infection when inhaled. The human immune system targets these particles for destruction based on their H and N sequences, and flu viruses constantly evolve the sequence of amino acids in these proteins to evade detection.

Most flu vaccines are produced with a decades-old process that involves culturing viruses in hundreds of millions of chicken eggs. Because the strain of flu that infects people is often difficult to grow in eggs, vaccine producers must make compromises to produce enough egg-based vaccine in time for fall flu shots. Unintended effects of this process have reduced vaccine efficacy against H3N2 the past two years, Deem said.

"Very often there are egg adaptations," he said. "There were a couple of these in the vaccine strain the past two seasons that wound up making it a little bit different from the actual circulating virus strain."

While other papers have examined these mutations using expensive and time-consuming experiments on live ferrets and laboratory cell cultures, Deem and Melia Bonomo used the pEpitope method to rapidly calculate how much the egg-passage mutations would decrease vaccine efficacy in humans.

"In fact, it's pretty substantial," said Bonomo, a doctoral student in applied physics. "The original strain used as a reference for the vaccine was basically a perfect match to the dominant circulating strain, and the predicted efficacy would have been around 47 percent. We found that the mutations in two amino acids out of more than 300 in one key region of the hemagglutinin protein were enough to lower efficacy to 19 percent against all circulating strains."

Deem said egg adaptations like those that reduced the efficacy of vaccines in 2016 and 2017 are unavoidable as long as flu vaccines are produced in eggs. He and Bonomo compared the efficacy of the egg-based vaccine with an experimental vaccine produced from insect cells via reverse genetics. The cell-based vaccine, which did not have the egg-passage mutations, had a predicted efficacy of 47 percent, the average value of a perfectly matched H3N2 vaccine, Deem said.

For decades, scientists have relied upon ferret models to gauge how flu viruses and flu vaccines will behave in people. But Deem said ferret studies over the past 10 years have been considerably less predictive of human effects than they were in the preceding three decades, and it is unclear why.

"It's been apparent over the last 10 years that egg adaptations have affected the efficacy of flu vaccines," he said. "It's also been apparent that the ferrets have done a really bad job of predicting the reduction of the efficacy due to the egg adaptations. Additionally, it's been difficult to get data from ferrets because the ferrets' immune systems have not recognized the vaccines particularly well over the past 10 years."

Deem said the ferret-based measures are one-third as predictive as the pEpitope method that has consistent performance over decades of flu data.

"When we look at our model over all data and over the last 10 years, we get the same answer," Deem said. "Whether we use the last 10 years of data or the last 50 years, our theory is very robust."

*The DOI of the* Clinical Infectious Diseases *paper is: 10.1093/cid/ciy323*
*A copy of the paper is available at: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy323/4972858*

***http://bit.ly/2HChnF5***

# Why More Vitamin D May Not Always Be a Good Thing

***More may not always be better when it comes to vitamin D.***

**By Rachael Rettner, Senior Writer | April 19, 2018 06:36am ET**

A new study from Denmark finds that high levels of vitamin D in the blood are linked with an increased risk of some cancers — but a decreased risk of others. Specifically, the researchers found that high vitamin D levels were linked with an increased risk of skin, prostate and blood cancers, and a decreased risk of lung cancer.

The study found only an association; it cannot prove that high vitamin D levels cause or prevent certain cancers. Nor can the study determine the precise reason for these seemingly contradictory effects on cancer risk.

But the researchers hope the findings draw attention to the possibility that high vitamin D levels aren't always a good thing. Until now, much of the research on vitamin D and cancer has been focused on the effects of low vitamin D levels, said study lead author Dr. Fie Juhl Vojdeman, of the Department of Clinical Biochemistry at Bispebjerg Frederiksberg Hospital in Copenhagen, Denmark.

People "have the impression that they can eat all the [vitamin D supplements] they want without any concerns," Vojdeman told Live Science. "However, we actually don't know whether it could be harmful in the long run to use heavy doses of [vitamin D supplements] if you do not have a critically low level in the blood." Vojdeman said more research is needed on the links between high vitamin D levels and cancer. The findings were presented Monday (April 16) at the American Association for Cancer Research meeting in Chicago and have not yet been published in a peer-reviewed journal.

For the study, the researchers analyzed data from more than 200,000 people living in the Capital Region of Denmark (a region in eastern Denmark) who had their blood vitamin D levels measured between April 2004 and January 2010. (Specifically, the researchers looked at the levels of 25OH vitamin D, or 25-hydroxyvitamin D, a metabolite of

the vitamin that's used as a measure of its levels in the body.) None of the participants had been diagnosed with cancer prior to their vitamin D test. The participants were followed for up to 10 years.

The average vitamin D measurement was about 50 nanomoles per liter (nmol/L). Normal levels are between 50 and 125 nmol/L (or 20 to 50 nanograms/milliliter), according to the National Institutes of Health's Office of Dietary Supplements.

During the study follow-up period, more than 18,000 people in the study were diagnosed with cancer. The study found that every 10 nmol/L increase in blood vitamin D was associated with a 9-percent increase in the risk of nonmelanoma skin cancer, a 10-percent increase in the risk of melanoma, a 5-percent increase in the risk of prostate cancer and a 3-percent increase in the risk of blood cancers.

But every 10 nmol/L increase in blood vitamin D was also linked with a 5-percent decrease in the risk of lung cancer.

The study was not designed to examine the mechanism behind these links, Vojdeman noted. One possibility, however, is that the higher risk of skin cancer is related to people's sun exposure. (People's bodies make vitamin D when exposed to sunlight, but too much sun exposure can lead to skin cancer.) However, Vojdeman said the study did not have data on the participants' sun protection.

Some studies have also found that the active metabolite of vitamin D, called calcitriol, has an immune suppressive effect that's also seen in some cancers, Vojdeman said. So, "theoretically, the higher level of vitamin D could reflect a more suppressive immune regulatory environment" that's linked with cancer, Vojdeman said. However, she stressed that this idea is "purely speculative at the moment."

In contrast, in studies in lab dishes, calcitriol has also been shown to counteract the effects of smoking on a type of lung cell, which might possibly explain the link with a reduced risk of lung cancer. But again, this idea needs more research.

Ultimately, "there is a need for more studies on the effects of high levels of … vitamin D on cancer at the mechanistic level," Vojdeman said.

***https://nyti.ms/2vx8lV6***

# Bodies Remodeled for a Life at Sea

***Scientists are discovering instances of human evolution in just the past few thousand years***

**Carl Zimmer**

We are the products of evolution, and not just evolution that occurred billions of years ago. As scientists peer deeper into our genes, they are discovering instances of human evolution in just the past few thousand years.

***A Bajau diver spearfishes in Sulawesi. A study suggests these sea-dwelling people have evolved adaptations to deep diving.*** **Credit Melissa Ilardo**

People in Tibet and Ethiopian highlands have adapted to living at high altitudes, for example. Cattle-herding people in East Africa and northern Europe have gained a mutation that helps them digest milk as adults.

On Thursday in the journal Cell, a team of researchers reported a new kind of adaptation — not to air or to food, but to the ocean. A group of sea-dwelling people in Southeast Asia have evolved into better divers.

The Bajau, as these people are known, number in the hundreds of thousands, scattered in communities in Indonesia, Malaysia and the Philippines. They have traditionally lived on houseboats; in recent times, they've also built houses on stilts in coastal waters.

"They are simply a stranger to the land," said Rodney C. Jubilado, a University of Hawaii anthropologist who studies the Bajau but was not involved in the new study.

Dr. Jubilado first encountered the Bajau while growing up on Samal Island in the Philippines. They made a living as divers, spearfishing or harvesting shellfish. "We were so fascinated that they could stay underwater much longer than us local islanders," Dr. Jubilado said. "I could see them literally walking under the sea."

Even as anthropologists study Bajau culture, biologists have grown curious about them, too. Bajau divers been observed plunging more than 200 feet underwater, their only protection a pair of wooden goggles — a physiological marvel.

In 2015, Melissa Ilardo, then a graduate student in genetics at the University of Copenhagen, heard about the Bajau. She wondered if centuries of diving could have led to the evolution of traits that made the task easier for them. “It seemed like the perfect opportunity for natural selection to act on a population,” said Dr. Ilardo.

Her first step was to travel to Sulawesi, Indonesia, and then to a coral reef island where she reached a Bajau village. After she proposed her study, they agreed to the plan. She returned a few months later, this time with a portable ultrasound machine to measure the size of the Bajau people’s spleens.

***Dr. Melissa Ilardo taking an ultrasound scan of a Bajau diver’s spleen. Scientists have found that marine mammals with larger spleens can dive deeper — the enlarged spleen acts much like a bigger scuba tank.*** **Credit Peter Damgaard**

When people plunge into water, they respond with the so-called diving reflex: the heart rate slows and blood vessels constrict as a way to shunt blood to vital organs. The spleen also contracts, squirting a supply of oxygen-rich red blood cells into the circulation.

All mammals have a diving reflex, but marine mammals like seals have a particularly strong one. Scientists suspect that the reflex helps them dive deeper — as it turns out, seals with bigger spleens can dive deepest. An enlarged spleen seems to function like a bigger scuba tank.

Dr. Ilardo scanned the abdomens of the Bajau villagers and then traveled about 15 miles inland to a village occupied by farmers known as the Saluan. She scanned them, too. When Dr. Ilardo compared scans from the two villages, she found a stark difference. The Bajau had spleens about 50 percent bigger on average than those of the Saluan.

Yet even such a remarkable difference might not be the result of evolution. Diving itself might somehow enlarge the spleen. There are plenty of examples of experience changing the body, from calloused feet to bulging biceps.

Only some Bajau are full-time divers. Others, such as teachers and shopkeepers, have never dived. But they, too, had large spleens, Dr. Ilardo found. It was likely the Bajau are born that way, thanks to their genes.

***Bajau homes built on stilts. Only some Bajau are full-time divers, while others are teachers and shopkeepers, but Dr. Ilardo found that all Bajau had enlarged spleens.*** **Credit Melissa Ilardo**

On her visit to Sulawesi, Dr. Ilardo also took mouth swabs from the Bajau and Saluan from which she extracted DNA. She looked at the genetic variations in each village and compared them to people from neighboring countries, such as New Guinea and China.

A number of genetic variants have become unusually common in the Bajau, she found. The only plausible way for this to happen is natural selection: the Bajau with those variants had more descendants than those who lacked them.

One variant of a gene called PDE10A influenced the size of spleens in the Bajau. People with one copy of the mutant gene had bigger spleens than those with none. People with two copies had even bigger spleens.

Scientists had never found a special role for PDE10A in the spleen. “This connection was a bit bizarre,” Dr. Ilardo said.

But there’s one possible link. PDE10A has been shown to control the level of thyroid hormone in the body. And scientists have found that injecting thyroid into mice with stunted spleens can make the organs grow larger.

Still, that wouldn't pin down exactly how PDE10A became so common in the Bajau. "It's the question that's harder than others," said Rasmus Nielsen, a geneticist at the University of California, Berkeley, who collaborated with Dr. Ilardo. For her own part, Dr. Ilardo suspects that natural selection favored the Bajau variant of PDE10A because deep diving is so risky. "I would think, as morbid as it is, that if they didn't have this, it would kill them," she said.

François-Xavier Ricaut, an anthropologist at the University of Toulouse who was not involved in the study, said that it wasn't clear yet how quickly this evolutionary change happened.

Some researchers suspect the Bajau only began diving to great depths when a market for sea cucumbers opened up in China in the 1600s. Or perhaps the adaptation began thousands of years earlier, at the end of the Ice Age, when rising sea levels turned the region around Indonesia into islands. "This study acts as a cornerstone for exciting questions to follow," said Dr. Ricaut.

Dr. Ilardo said there were likely a number of other genes that help the Bajau dive. She and her colleagues also found evidence for natural selection on a gene called BDKRB2.

In a study published last year, Russian scientists discovered that it plays a role in the diving reflex. In people with variants of BDKRB2, blood vessels are more tightly constricted when they plunge their faces into cold water. To see if that's the case with the Bajau, Dr. Ilardo will need to take another trip to beautiful Sulawesi. "I would be happy doing this as long as I can," she said.

***http://bit.ly/2K31qGd***

## Doctors tried to lower $148K cancer drug cost; makers triple price of pill

***"That got us kind of p---ed off," doctor said after learning of price jump.***

**Beth Mole - 4/20/2018, 1:48 AM**

A drug that treats a variety of white blood cell cancers typically costs about $148,000 a year, and doctors can customize and quickly adjust doses by adjusting how many small-dose pills of it patients should take each day—generally up to four pills. At least, that was the case until now.

Last year, doctors presented results from a small pilot trial hinting that smaller doses could work just as well as the larger dose—dropping patients down from three pills a day to just one. Taking just one pill a day could dramatically reduce costs to around $50,000 a year. And it could lessen unpleasant side-effects, such as diarrhea, muscle and bone pain, and tiredness. But just as doctors were gearing up for more trials on the lower dosages, the makers of the drug revealed plans that torpedoed the doctors' efforts: they were tripling the price of the drug and changing pill dosages.

The drug, ibrutinib (brand name Imbruvica), typically came in 140mg capsules, of which patients took doses from 140mg per day to 560mg per day depending on their cancer and individual medical situation. (There were also 70mg capsules for patients taking certain treatment combinations or having liver complications.) The pills treat a variety of cancers involving a type of white blood cell called B cells. The cancers include mantle cell lymphoma, which was approved for treatment with four 140mg pills per day, and chronic lymphocytic leukemia, approved to be treated with three 140mg pills per day. Each 140mg pill costs somewhere around $133—for now.

Imbruvica's makers, Janssen and Pharmacyclics, have now gotten approval to sell four different tablets of varying strengths: 140mg, 280mg, 420mg, and 560mg. But the new pills will all be the same price—around $400 each—even the 140mg dose pill. The makers will stop selling the old, cheaper 140mg pill within three months, according to a report by the *Washington Post*.

The plan nixes any chance to lower costs with lower dosages. Even if patients can drop down to just 140mg a day, they'll pay three times what they pay now for each 140mg pill.

**"Kind of pissed off"**

In a statement to the *Post*, Janssen and Pharmacyclics explained the move by saying the new line-up is "a new innovation to provide patients with a convenient one pill, once-a-day dosing regimen and improved packaging, with the intent to improve adherence to this important therapy." They noted that those taking 560mg a day will save money with the new pricing.

But doctors balked at what they saw as an underhanded move. In an interview with the *Post*, oncologist Mark Ratain of the University of Chicago Medicine put things bluntly: "That got us kind of pissed off."

Ratain and colleagues wrote a commentary in the weekly newsletter *Cancer Letters* this month, decrying the price hike and new pill series, calling it "highly unusual." In addition to thwarting efforts to help lower treatment costs, the doctors pointed out that the new dosage lineup will make it harder to nimbly adjust patients' doses by simply advising them to take different numbers of pills each day. Switching a patient from a 280mg or 420mg per day dose down to 140mg will require paperwork, filling a new prescription, and having patients return unused pills—a process that can drag out for weeks. And increasing a patient's dose would either be just as lengthy of a process or risk multiplying their treatment costs even further by doubling or tripling the pills each day.

In their commentary, titled in part "Sales Revenues at the Potential Expense of Patient Safety," the doctors lay out examples of when quick dosage changes would be necessary. Those include when a patient needs to drop down while they're on a short course of antibiotics or to adjust for new combination-cancer treatments. "Any putative convenience advantage of taking one pill a day is negated by the marked inconvenience to the patient of having to return pills every time there is a need for a dosage change," they write.

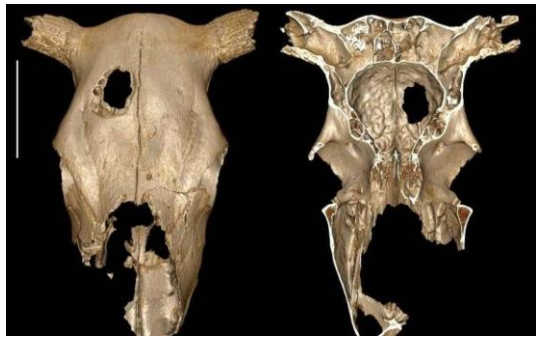
Ratain and colleagues end with a call to the Food and Drug Administration to look into the matter, "given that it creates a barrier to optimal prescribing for some patients," they write. "We further urge the FDA to recognize that the combination of the high price per pill and the flat pricing scheme are specific impediments to safe administration, and that ignoring the marketing approach for ibrutinib is antithetical to fostering optimally safe dosing and administration."

***http://bit.ly/2vyDQhx***

## Holey cow! Evidence of Stone Age veterinary 'surgery'

***A hole in the skull of a Stone Age cow was likely made by humans about 5,000 years ago, probably by a primitive veterinarian or trainee surgeon, scientists said Thursday.***

**April 19, 2018 by Pascale Mollard**



***This handout picture shows a 3D reconstruction of a cow skull with a hole produced by trepanation.***

The hole appears to have been painstakingly carved into the animal's head, but whether it was an operation to save the cow or practice for surgery on humans, was not clear, a duo of anthropologists reported in the journal *Scientific Reports*.

Either way, the puncture does seem to represent the earliest known example of veterinary "trepanation"—the boring of a hole into the skull, they said.

"There are many Neolithic (human) skulls in Europe which bear the marks of trepanation. But we have never seen it in animals," co-author Fernando Ramirez Rozzi of France's CNRS research institute told AFP.

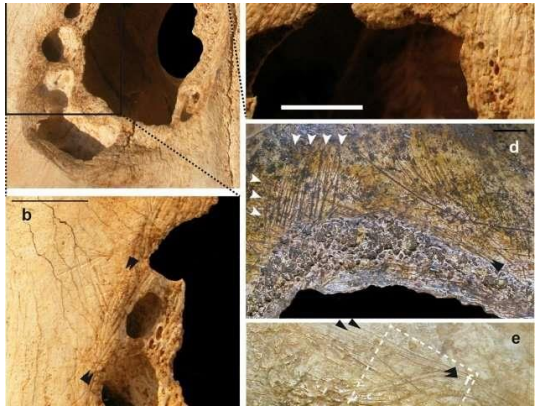
The Neolithic era was the closing chapter of the Stone Age—a time when prehistoric humans, hunter-gatherer nomads until then, first tried their hand at cultivating crops and building permanent villages.

The cow skull comes from an archaeological site in western France, inhabited by a Stone Age community between 3,400 and 3,000 BC.

Bone fragments scattered around the camp showed that cows were the main source of food, along with pigs, sheep, and goats.

It was thought at first that the matchbox-sized hole was made when the cow was gored by a horned rival in a fight.

But on closer inspection with high-definition scanners, the team found no splintering or fractures consistent with such a strong blow. The puncture was too regular to have been the work of a gnawing pest, nor did it appear to have been made by a tumour or infectious disease, such as syphilis or tuberculosis, as the skull showed no other signs of sickness.




***This picture shows cut marks in a cow skull (a, b, c) and in a human skull (d, e) from the Neolithic period suggesting that the technique used for the trepanation in humans is the same as that employed in the cow skull.***

## Dead or alive?

Religious ritual also seemed an unlikely explanation, as the skull was thrown away with the rubbish. Cut- and scrape marks were found around the hole, said Rozzi—similar to those seen on Neolithic human skulls into which holes had been bored.

"I believe that the evidence of trepanation is indisputable," the researcher added. "It is the only possible explanation."

But why would a Stone Age human operate on an animal?

"There are two possible explanations," according to Rozzi. "Either they were treating the cow, or they were practicing on it before trying their hand at surgery on humans."

The first option seemed unlikely, he added, given that cows were in such abundance. The team could not determine whether the hole was made while the cow was still alive, or after it died. The bone, however, had not started regrowing around the hole, which showed the cow either did not survive the operation, if there was one, or was cut post-mortem.

***More information:*** *Fernando Ramirez Rozzi et al. Earliest Animal Cranial Surgery: from Cow to Man in the Neolithic, Scientific Reports (2018).* *DOI: 10.1038/s41598-018-23914-1*

***http://bit.ly/2HhtkAp***

# How Many Genes Do Cells Need? Maybe Almost All of Them

***An ambitious study in yeast shows that the health of cells depends on the highly intertwined effects of many genes, few of which can be deleted together without consequence.***

**Veronique Greenwood Contributing Writer**

By knocking out genes three at a time, scientists have painstakingly deduced the web of genetic interactions that keeps a cell alive. Researchers long ago identified essential genes that yeast cells can't live without, but new work, which appears today in *Science*, shows that looking only at those gives a skewed picture of what makes cells tick: Many genes that are inessential on their own become crucial as others disappear. The result implies that the true minimum number of genes that yeast — and perhaps, by extension, other complex organisms — need to survive and thrive may be surprisingly large.

About 20 years ago, Charles Boone and Brenda Andrews decided to do something slightly nuts. The yeast biologists, both professors at the University of Toronto, set out to systematically destroy or impair the genes in yeast, two by two, to get a sense of how the genes functionally connected to one another. Only about 1,000 of the 6,000 genes in the yeast genome, or roughly 17 percent, are considered essential for life: If a single one of them is missing, the organism dies. But it seemed that many other genes whose individual absence was not enough to spell the end might, if destroyed in tandem, sicken or kill the yeast. Those genes were likely to do the same kind of job in the cell, the biologists reasoned, or to be involved in the same process; losing both meant the yeast could no longer compensate.

Ignorant as science may still be about certain happenings in yeast, it's dwarfed by our ignorance of what is going on in our own cells

Boone and Andrews realized they could use this idea to figure out what various genes were doing. They and their collaborators went about it deliberately, by first generating more than 20 million strains of yeast

that were each missing two genes — almost all of the unique combinations of knockouts among those 6,000 genes. The researchers then scored how healthy each of the double mutant strains was and investigated how the missing genes could be related. The results let the researchers sketch a map of the shadowy web of interactions that underlie life. Two years ago, they reported the details of the map and revealed that it had already allowed researchers to discover previously unknown roles for genes.

Along the way, however, they realized that a surprising number of genes in the experiment didn't have any obvious interactions with others. "Maybe, in some cases, deleting two genes isn't enough," Andrews said, reflecting on their thoughts at the time. Elena Kuzmin, a graduate student in the lab who is now a postdoc at McGill University, decided to go one step further by knocking out a third gene.

In the paper out today in *Science*, Kuzmin, Boone, Andrews and their collaborators at the University of Toronto, the University of Minnesota and elsewhere report that effort has yielded a deeper and more detailed map of the cell's inner workings. Unlike in the double mutant experiments, the researchers did not make every possible combination of mutations — there are about 36 billion different ways to knock out three genes in yeast. Instead, they looked at the pairs of genes they'd already knocked out and ranked their interactions according to severity. They took a number of those pairs, whose effects ranged from making cells grow a little slower to making them significantly impaired, and matched them up one by one with knockouts of other genes, generating about 200,000 triple mutant strains. They monitored how quickly colonies of the mutant yeast grew, and after noting which mutants were struggling, they checked databases to see what the disabled genes were thought to do.

As the scientists built their new map, several things became clear. For one, in about two-thirds of the triple mutants that showed an additional genetic interaction, knocking out the third gene tended to intensify the problems that the double mutant had. Pairs of genes might already show some interaction with each other, Andrews said, "but it was much more severe when we deleted a third gene." Boone says that these are likely to be situations in which the loss of a third gene is dealing a critical blow to an already faltering system.

However, a third of the interactions were completely new. And they tended to involve more disparate processes. In double mutants, the functional connections between genes tended to be tight: A gene involved in DNA repair usually had links with other genes that are also involved in DNA repair, and genes that had interactions with each other usually interacted with the same other genes. With the triple mutants, however, more far-flung tasks started to get linked together. The constellation of connected cellular tasks shifted and morphed subtly.

"Perhaps what we're sampling here," Andrews said, "are some functional connections in the cell that we weren't able to see before."

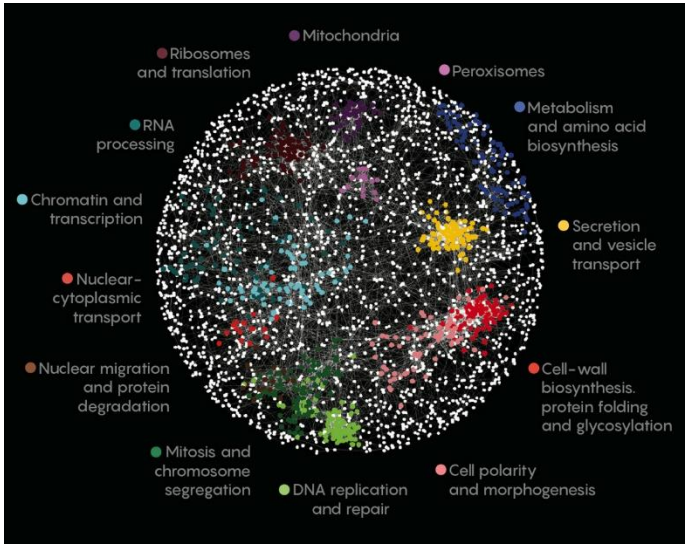
One set of new connections, for example, was between genes involved in transporting proteins and genes involved in DNA repair. On the surface, it's difficult to see what would connect these two functions. And in fact, the researchers still don't have a mechanistic explanation. But they are sure there is one. "Our immediate reaction was, 'Well, that's kind of random,'" Andrews said. "But we've learned over the course of doing this project that it's not random. We just don't understand how the cell is connected."

Their group has just started probing that link between protein transport and DNA repair, but according to Andrews, if you look closely at those yeast cells, they do in fact show a great deal of DNA damage. The map of connections helped draw their attention to it: "There would have been no reason to look before," she said.

Yeast geneticists were never under the impression that only essential genes mattered. But the new paper reinforces the idea that simplistic interpretations of just what is important in the yeast genome are likely to be flawed. The reality is more complicated, Boone and Andrews say. They suggest that when double and triple interactions are taken into account, the number of genes that a yeast cell truly can't do without

jumps. As their paper notes, the minimum genome needed for yeast cells to avoid a substantial defect "may nearly approach the complete set of genes encoded in the genome."

Indeed, experimental efforts to devise a minimal genome for a microorganism — to pinpoint the smallest number of genes that a cell would need to survive, as a step toward making artificial genomes — have shown it to be surprisingly difficult to remove genes and still have a thriving creature.




***This figure maps the interactions among various genes (represented as dots) in the yeast genome. Genes with linked effects are connected by lines; genes with more strongly correlated effects are closer together. The color of the dots corresponds to the biological processes and organelles in which the genes are involved.*** **Raamesh Deshpande**

In 2016, researchers at the J. Craig Venter Institute (JCVI) reported the creation of an artificial genome for the bacterium *Mycoplasma genitalium*, in which they winnowed its 525 genes down to 473. But negative effects from removing seemingly inessential genes were indeed a serious issue, according to Clyde A. Hutchison III, a biochemist and distinguished professor at JCVI involved in the work. "That was the main problem for choosing a gene set to design for a minimal genome," he said.

Joel Bader, a systems biologist at Johns Hopkins University, says that the current work suggests an intriguing connection to an idea in human genetics — that a wide array of genes may be subtly influencing traits that we don't normally associate with them. "[The] closer we are able to look, the more we are able to see that perturbing one gene or pathway has effects that propagate throughout the entire system," he said. "The effects get weaker, but they can still be measured."

Ignorant as science may still be about certain happenings in yeast, it's dwarfed by our ignorance of what is going on in our own cells. Part of what makes a project like this one at the University of Toronto possible is that yeast has been heavily studied and its genes intricately annotated by several generations of biologists, to a degree not yet reached with the human genome, which is comparatively enormous, rambling and full of mysteries. Still, the researchers say that they hope that as gene-editing technology for human cells advances, these kinds of experiments can help reveal more about the workings of cells and how the genes within a genome relate to one another. "I think there are many basic rules of genome biology we have not discovered," Andrews said.

***http://bit.ly/2F7lTpJ***

## A study links soil metals with cancer mortality

### *Associations found between heavy metals in soils and types of cancer*

Spanish epidemiologists and geologists have found associations between esophageal cancer and soils where lead is abundant, lung cancer and terrains with increased copper content, brain tumor with areas rich in arsenic, and bladder cancer with high cadmium levels. These statistical links do not indicate that there is a cause-effect relationship between soil type and cancer, but they suggest that the influence of metals from the earth's surface on the geographical distribution of tumors should be analyzed.

The risk of dying from cancer is not the same in all geographic regions. There are many factors that influence, including the type of soil, since it can harbor heavy metals and semimetals that are carcinogenic for humans. The chronic exposure of a population to these toxic elements, which enter the body through the food chain and food, could increase the frequency of certain tumors in some territories.

In this context, researchers from the National Epidemiology Center of the Carlos III Health Institute (ISCIII) and the Geological and Mining Institute of Spain (IGME) have jointly assessed the possible statistical association between the concentrations of heavy metals in the soil and mortality by different cancer types. The results have been published in the open access journals Environmental Geochemistry and Health and Environmental Science and Pollution Research International.

The data has been extracted from the Spain´s Geochemical Atlas, published by the IGME in 2012, as well as from a database with 861,440 deaths from 27 cancer types that occurred in almost 8,000 Spanish municipalities between 1999 and 2008. The data can be extrapolated to the present because the geochemical composition of the soil is stable and the mortality patterns for this disease usually do not vary.

The authors have crossed the information of the type of soil and the geographic distribution of the tumors, applying statistical analyzes and taking into account the presence of local polluting foci or socio-demographic variables that could interfere in the results.

They have found various associations, such as increased mortality in both genders from esophageal cancer in areas with higher concentrations of lead, and lung cancer in areas with high copper levels. "We have also detected that the highest of cadmium, lead, zinc, manganese and copper concentrations in the soil are statistically associated with a higher mortality due to cancers of the digestive system in men," explains Pablo Fernández, ISCIII researcher and co-author of the paper, "and in the case of women, a higher mortality from brain cancer in those areas with more cadmium content".

The results also show a relationship between soils with more cadmium and higher mortality from bladder cancer; as well as lands with high concentrations of arsenic and more cases of death from brain tumors.

"This research suggests that the geochemical composition of the soil, especially its metals, could be influencing the spatial distribution and mortality patterns of cancer in Spain, regardless of the socio-demographic context," says Fernández, who highlights "the great contribution of this work to environmental epidemiology and public health in general".

"However," he adds, "although it is plausible that the contents of toxic elements in the soil, even if they are very small, may be a component in the cancer etiology, the results must be interpreted with great caution, since the relationships found do not allow to conclude that there is a cause-effect relationship. Our study does not have individual exposure data or information about other very important factors in the origin of cancer, such as tobacco, alcohol consumption or obesity".

Gonzalo López-Abente, another of the co-authors and also researcher at ISCIII, agrees: "The conclusions move in the field of hypotheses and statistical associations, which will have to be confirmed with future analyzes to check whether the composition of the soil itself has its counterpart in the biological markers of humans. In any case, the results are plausible and we could be facing one more component of the cancer etiology".

*Gonzalo López-Abente, Juan Locutura-Rupérez, Pablo Fernández-Navarro, Iván Martín-Méndez, Alejandro Bel-Lan, Olivier Núñez. "Compositional analysis of topsoil metals and its associations with cancer mortality usings patial misaligned data". Environmental Geochemistry and Health 40(1): 283-294, 2018.*

*Olivier Núñez, Pablo Fernández-Navarro, Iván Martín-Méndez, Alejandro Bel-Lan, Juan F. Locutura Rupérez, Gonzalo López-Abente. "Association between heavy metal and metalloid levels in topsoil and cancer mortality in Spain". Environmental Science and Pollution Research 24(8): 7413-7421, 2017.*

*The researchers of the Carlos III Health Institute who have participated in this study belong to the Cancer and Environmental Epidemiology Area of the National Center of Epidemiology of ISCIII, which also belongs to the Biomedical Research Network in Epidemiology and Health Consortium (CIBERESP).*

***https://nyti.ms/2K3bE9s***

## F.D.A. Panel Recommends Approval of Cannabis-Based Drug for Epilepsy

***A Food and Drug Administration advisory panel on Thursday unanimously recommended approval of an epilepsy medication made with an ingredient found in marijuana.***

**By Sheila Kaplan**

WASHINGTON — If the agency follows the recommendation, as is expected, the drug would be the first cannabis-derived prescription medicine available in the United States.

The drug, called Epidiolex, is made by GW Pharmaceuticals, a British company. Its active ingredient, cannabidiol, also called CBD, is one of the chemical compounds found in the cannabis plant, but it does not contain the properties that make people high.


***The drug's active ingredient, cannabidiol, is one of the chemical compounds found in the cannabis plant but it does not make people high.*** **Kathy Young/Associated Press**

That makes it different from the "medical marijuana" allowed by a growing number of states. In those cases, certain patients are legally authorized to smoke or ingest marijuana to treat severe pain, nausea and other ailments.

There are already several drugs on the market that are derived from synthetic versions of THC and other chemicals of the cannabis plant, generally used to ease nausea in cancer patients, and to help AIDS patients avoid weight loss.

Advocates for development of marijuana-based treatments, and those pushing for better treatments of epilepsy, were pleased with the panel's recommendation.

"This is a very good development, and it basically underscores that there are medicinal properties to some of the cannabinoids," said Dr. Igor Grant, director of the Center for Medicinal Cannabis Research at the University of California San Diego. "I think there could well be other cannabinoids that are of therapeutic use, but there is just not enough research on them to say."

The panel recommended approval of the drug to treat two rare forms of epilepsy — Lennox-Gastaut syndrome and Dravet syndrome. They are among the most difficult types of epilepsy to treat, with nearly all patients continuing to have seizures despite currently available medications, according to the F.D.A. The large number of seizures — experts say a person can have multiple episodes a day — puts children at high risk for intellectual and developmental disabilities, as well as death. Lennox-Gastaut syndrome usually appears between ages 3 and 5, and Dravet syndrome earlier.

There are an estimated 30,000 children and adults with Lennox-Gastaut syndrome and fewer than that with Dravet syndrome. Because the conditions are so rare, GW Pharmaceuticals has received an orphan drug designation for Epidiolex.

"It's very important that we have additional treatments because these patients have very, very difficult to control seizures," said Dr. Jerzy P. Szaflarski, a neurology professor at the University of Alabama at Birmingham, who directs the university's epilepsy division. "I get questions about cannabidiol almost every day."

The briefing materials prepared for the committee by F.D.A. staff made it clear that the agency supports the application. The F.D.A. wrote that GW Pharma had submitted positive results of efficacy from three randomized, double-blind, placebo-controlled trials conducted in patients with both diseases.

"The statistically significant and clinically meaningful results from these three studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS," the agency noted. The briefing papers also reported risk of a potentially serious side effect — liver injury — but said it could be managed.

Epidiolex would be the first of a new class of drugs to treat epilepsy. The F.D.A. is not bound by advisory committee recommendations but often follows them.

Christina SanInocencio, a nurse and founder of the LGS Foundation, hopes it does. "I have a brother with the disorder," Ms. SanInocencio said. "I've met hundreds and hundreds of families who have kids living with it. It's so devastating. Any new medicine that comes to the market is a really big win for our community."

http://bit.ly/2vvC2FQ

# Correcting tiny differences in patient's position for radiotherapy could increase survival chances

***Very small differences in the way a patient lies during radiotherapy treatment for lung or oesophageal cancer can have an impact on how likely they are to survive, according to research presented at the ESTRO 37 conference.***

Barcelona, Spain: These differences of only a few millimetres can mean that the radiation treatment designed to target patients' tumours can move fractionally closer to the heart, where it can cause unintentional damage and reduce survival chances.

The finding suggests that survival could be improved by tightening up treatment guidelines to ensure patients are positioned more accurately.

Radiotherapy plays an important role in cancer care in, amongst others, hard to treat tumours such as lung and oesophageal cancer. However, it can cause side-effects and previous research shows that radiotherapy to the chest can have negative long-term effects on the heart, for example, increasing the risk of heart disease.

When planning radiotherapy treatment, cancer specialists create a CT image of their patient. This reveals the exact position and size of the tumour within the body. At each subsequent treatment, another image is created and used to check that the patient and, therefore, the tumour is in the same position, within a certain threshold, before the treatment is delivered.

The new research was presented by Corinne Johnson, a medical physics PhD student at the Manchester Cancer Research Centre, part of the Christie NHS Foundation Trust and the University of Manchester, UK.

She and her colleagues studied a group of 780 patients with non-small cell lung cancer who were treated with radiotherapy. For each treatment, patients were positioned on the treatment machine and an image was taken to confirm that they lay within 5mm of their original position. They used the data from these images to gauge how accurately the radiotherapy dose was delivered over the course of treatment, and whether it was shifted slightly closer or slightly further away from the patient's heart.

When they compared these data with how likely patients were to survive, they found that patients with slight shifts towards their hearts were around 30 per cent more likely to die than those with similar sized shifts away from their hearts.

When they repeated the research with a group of 177 oesophageal cancer patients, they found an even greater difference of around 50 per cent. In both groups the pattern of survival remained even when researchers took other factors such as the patient's age into account.

Johnson explains: "We already know that using imaging can help us to target cancers much more precisely and make radiotherapy treatment more effective.

"This study examines how small differences in how a patient is lying can affect survival, even when an imaging protocol is used. It tells us that even very small remaining errors can have a major impact on patients' survival chances, particularly when tumours are close to a vital organ like the heart.

"By imaging patients more frequently and by reducing the threshold on the accuracy of their position, we can help lower the dose of radiation that reaches the heart and avoid unnecessary damage."

Johnson and her colleagues are now looking at the data in more detail to see whether particular regions of the heart are more sensitive to radiation than others, and they hope to investigate the effect of differences in patient position in other types of cancer.

President of ESTRO, Professor Yolande Lievens, head of the department of radiation oncology at Ghent University Hospital, Belgium, said: "Radiotherapy treatments are given according to strict protocols to ensure that patients get the most effective treatment with the fewest possible side-effects. This research suggests that changes to lung and oesophageal cancer protocols could positively impact the overall survival of patients with these cancers, both of which have relatively high mortality rates."

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