http://bit.ly/2VWQtim

Prostate cancer patients with gene mutation at three times the risk of dying

Largest ever study of advanced prostate cancer genomics reveals gene mutation identifying the most aggressive of prostate cancers

Scientists have identified a gene mutation in the tumours of men with prostate cancer that is linked to very poor survival - and which could be used to pick out patients for more intensive treatment.

Men with mutations in the retinoblastoma gene in their tumours were more than three times as likely to die and nearly seven times as likely to relapse on standard treatments as those without the gene.

The retinoblastoma gene, known as RB1, is so called because mutations in it cause a rare children's eye cancer of the same name and is known to play a central role in stopping healthy cells from dividing uncontrollably.

Researchers at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust believe testing men for the mutation could identify those with especially aggressive disease who need the most intensive available treatments. They are also studying new ways to treat patients with the high-risk gene.

The researchers, along with colleagues in the US and Europe, looked in detail at the DNA sequence, the activity of genes and how the tumours looked under the microscope in 444 tumours samples from 429 men with advanced prostate cancer.

Their study is published today (Monday) in the Proceedings of the National Academy of Sciences (PNAS), and was funded by the Prostate Cancer Foundation and Stand Up to Cancer.

The team wanted to identify which of the many genes linked to prostate cancer were the most important indicators of patient survival and response to the standard treatments abiraterone and enzalutamide.

Patients with mutations in the RB1 gene in their tumours were 3.3 times more likely to die and 6.6 times more likely to relapse during the course of the study than other men who also had standard treatment but did not have the mutation.

RB1 was the only gene found to have such an impact on survival, but mutations in two further genes - p53 and the androgen receptor gene - were associated with an increased risk of relapse on abiraterone or enzalutamide.

Mutations in DNA repair genes BRCA1, BRCA2 and ATM, and in PI3K genes were relatively common but had no impact on treatment with abiraterone or enzalutamide or on overall survival.

However, the research did identify clues for how some patients with prostate cancer could be treated more effectively using immunotherapy and a breast cancer treatment.

Men whose tumours had mutations in a gene linked to a good response to immunotherapy, CDK12, often also had mutations in the genes CDK4 and CCND1, which are the targets of a breast cancer drug called palbociclib.

That suggests that combining immunotherapy with palbociclib could be an effective treatment for this group of men.

Professor Johann de Bono, Regius Professor of Cancer Research at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation trust, said:

"Our study really got under the bonnet of prostate cancer to understand the 'engine' driving tumour growth and explore how a wide range of genes affect the disease and its response to treatment. We identified one particular genetic mutation that seems to indicate that tumours are going to be very aggressive, and that the affected men need the most intensive treatment we have available.

"Our research could also open up various new approaches to prostate cancer treatment, and offers the intriguing suggestion that some patients could benefit from immunotherapy alongside an

existing breast cancer drug. That's a great example of how genetic research can find the common links between cancers, and ensure research into one cancer type can also benefit patients with other tumours."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"There are a large number of genetic mutations present in a tumour, and working out their relative importance is crucial to deliver the best precision medicine to cancer patients.

"This exciting study has identified which features of advanced prostate tumours are the most important for treatment and survival - and has picked out one gene mutation in particular which has an especially serious adverse impact on how long patients live.

"The crucial thing now is that we make use of this information, by developing a test to identify affected men and to make sure they receive the best treatments we have available today, while also focusing our efforts on improving options for the future."

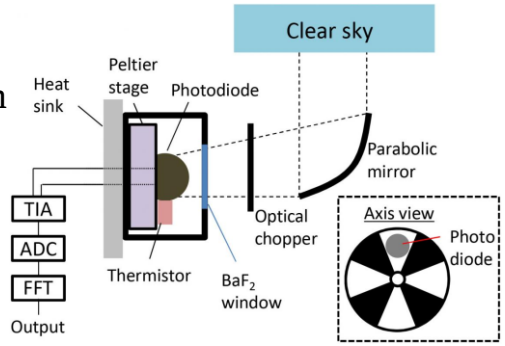
http://bit.ly/2LwvNcU

Experimental device generates electricity from the coldness of the universe

Using an infrared photodiode pointed to the sky, a new device harvests energy from the temperature difference between Earth and near absolute zero temperatures of deep space.

WASHINGTON, D.C. - The obvious drawback of solar panels is that they require sunlight to generate electricity. Some have observed that for a device on Earth facing space, which has a frigid temperature, the chilling outflow of energy from the device can be harvested using the same kind of optoelectronic physics we have used to harness solar energy. New work, in a recent issue of *Applied Physics Letters*, from AIP Publishing, looks to provide a potential path to generating electricity like solar cells but that can power electronics at night.

An international team of scientists has demonstrated for the first time that it is possible to generate a measurable amount of electricity in a diode directly from the coldness of the universe. The infrared semiconductor device faces the sky and uses the temperature difference between Earth and space to produce the electricity.



A drawback of solar panels is that they require sunlight to generate electricity. Some have observed that for a device on Earth facing space, the chilling outflow of energy from the device can be harvested using the same kind of optoelectronic physics we have used to harness solar energy. New work, in Applied Physics Letters, looks to provide a potential path to generating electricity like solar cells but that can power electronics at night. This is a schematic of the experimental infrared photodiode that has generated electricity directly from the coldness of space. **Masashi Ono**

"The vastness of the universe is a thermodynamic resource," said Shanhui Fan, an author on the paper. "In terms of optoelectronic physics, there is really this very beautiful symmetry between harvesting incoming radiation and harvesting outgoing radiation."

In contrast to leveraging incoming energy as a normal solar cell would, the negative illumination effect allows electrical energy to be harvested as heat leaves a surface. Today's technology, though, does not capture energy over these negative temperature differences as efficiently.

By pointing their device toward space, whose temperature approaches mere degrees from absolute zero, the group was able to find a great enough temperature difference to generate power through an early design. "The amount of power that we can generate with this experiment, at the moment, is far below what the theoretical limit is," said Masashi Ono, another author on the paper.

The group found that their negative illumination diode generated about 64 nanowatts per square meter, a tiny amount of electricity, but an important proof of concept, that the authors can improve on by enhancing the quantum optoelectronic properties of the materials they use.

Calculations made after the diode created electricity showed that, when atmospheric effects are taken into consideration, the current device can theoretically generate almost 4 watts per square meter, roughly one million times what the group's device generated and enough to help power machinery that is required to run at night. By comparison, today's solar panels generate 100 to 200 watts per square meter.

While the results show promise for ground-based devices directed to the sky, Fan said the same principle could be used to recover waste heat from machines. For now, he and his group are focusing on improving their device's performance.

The article, "Experimental demonstration of energy harvesting from sky using the negative illumination effect of a semiconductor photodiode," is authored by Masashi Ono, Parthiban Santhanam, Wei Li, Bo Zhao and Shanhui Fan. The article appeared in Applied Physics Letters *on April 23, 2019 (DOI: 10.1063/1.5089783). It can be accessed at http://aip.scitation.org/doi/10.1063/1.5089783.*

http://bit.ly/2JdAm9Y

Ancient Chinese Buildings Are Held Together With Rice, Sugar, and Blood

Edible additives in mortar served both practical and philosophical purposes.

by Claire Voon

The city wall of Nanjing, built 600 years ago, was the first line of defense for the founding capital of the Ming dynasty. Originally 22 miles long, it was built with 350 million bricks, most of which have survived centuries of weathering. In 2010, intrigued by the wall's sturdy composition, a team of Chinese researchers analyzed mortar samples from one section. The secret ingredient turned out to be humble sticky rice, a staple of Chinese cuisine.

This use of gummy grains as an adhesive is not entirely surprising. For thousands of years, Chinese builders mixed sticky rice, or glutinous rice, with lime mortar to assemble structures across the country, including city walls, pagodas, bridges, and tombs. Cooked rice was first boiled into a paste, then blended with sand and lime, a substance produced by heating limestone. According to researchers Yan-Bing Luo and Yu-Jie Zhang of Sichuan University, this starchy concoction "holds important status and value in Chinese architectural history." Because of its strength and low porosity, they refer to it as "Chinese concrete."

A section of the Great Wall, in Yanqing County, contains mortar made with blood. **Oleksandr Rupeta/NurPhoto/Getty Images**

Scientists have long been fascinated with this unusual formula, and in recent years, different teams have conducted studies to better understand it. Researchers Jiajia Li and Bingjian Zhang spent six years collecting 378 samples of ancient mortar from 159 sites throughout China, dating from the Taosi phase (2300-1900 BC) all the way to the late Qing dynasty (1644-1911). Their numerous chemical tests found that 219 mortars from 96 locations had "organic components"—that is, small traces of starch, protein, brown sugar, blood, and oil. These mixtures have helped preserve much of China's built landscape. As the researchers write, "the quality of mortar used in construction has played an important role in determining monument durability."

One notable sample, from a 2000-year-old tomb in Jiangsu province, turned up what the researchers say is the oldest known trace of sticky rice mortar. (A separate study identified an earlier

use, dating to three thousand years ago.) While the researchers don't know the recipe's origin story, they determined that by the Tang dynasty (816-907), rice was often used to improve construction. By the Song and Ming dynasties, both periods of extensive architectural activity, this unique mortar was prevalent, especially in the foundations of important buildings.

Sticky rice is sweet, and augments savory dishes such as *zongzi*, pyramids of rice and fillings neatly wrapped in leaves, or *tang yuan*, a sweet soup with rice dumplings. It is also waxy—a texture that comes from the polysaccharide amylopectin, which gives the rice a denser microstructure. Mixed with lime mortar, the grains boost compressive strength, helping walls bear loads without fracturing. They are also highly water resistant, which protects buildings against erosion.

Mortar samples from halls and the garden of the famed Forbidden City, built in the 15th century, tested positive for the starch. So did sections of the Great Wall of China, which was largely restored during the Ming dynasty. But one sample from the Wall, where it runs through Yanqing County, contained a less common ingredient: animal blood, which showed up in just five sites.

Researchers found sugar in the mortar of Suzhou's Tiger Hill Pagoda. Siyuwj/CC BY-SA 4.0

Animal blood might sound like a grisly substance for building walls, but it was a perfectly normal additive used by several cultures. Historical recipes written in French, Italian, and English have detailed ways to mix oxblood and lime mortars. In China, builders used pig blood to improve the consistency of their mortar, according to a 2014 study. It is also easily available, resulting in diverse regional dishes such as pork blood soup and pig blood curd.

Many other organic additives favored by the Chinese helped repel water. Li and Zhang found oil samples from 87 sites, which they believe to be tung oil, a common waterproof seal for wooden ships. Another, egg white, is not only water resistant but also improves the viscosity of mortar. (Eggs whites were also used as a paint binder to color the famous Terracotta Army.) Researchers have found that brown sugar, too, reduces water content in mortars, enhancing their strength. According to ancient literature, sucrose was often used to build forts and homes in eastern and southeastern China.

These mortars were also likely invented out of necessity. In distant Rome, the secret ingredient of concrete was volcanic ash, which improved the durability of lime mortar and enabled it to set underwater. Similar mortars made with volcanic ash were adopted throughout Europe and western Asia; however, volcanic ash was not available in ancient China. Instead, engineers would have used their own regional ingredients to create distinctive building materials. Other innovative mortars have similarly developed out of convenience, from a church in the Philippines made of egg whites to a Brazilian chapel held together by wine.

Great design is often the result of thinking beyond form and function. Philosophy, the researchers posit, might be one poetic inspiration for these fusion pastes. "Ancient Chinese people advocated a view of nature often termed 'heaven-and-human oneness,'" Li and Zhang write. "The use of agricultural, forestry, and animal products in building materials reflected architectural aesthetics that sought to integrate architecture and nature."

Incredibly, structures built with sticky rice mortar have survived more than natural erosion. A Ming tomb, of the minister Xu Pu and his wife, was nearly damaged by a bulldozer when found in 1978, but it was "so firm [the vehicle] could do nothing about it," according to a 2009 paper. Its three authors describe another near-

miracle: in 1604, when a 7.5-magnitude earthquake shook the port city of Quanzhou, many temples, stupas, and bridges were not destroyed. Instead, sticky rice mortar kept their foundations firmly secured.

Although clearly effective, these revolutionary adhesives fell out of fashion in the late Qing dynasty. Li and Zhang note that China's first cement factory opened in 1889 in Hebei province, and this inorganic binder gradually filled the role of composite mortars.

But researchers still see potential in these ancient formulas, especially to stabilize historical sites. Cement is detrimental to conservation work, writes Dr. Gaetano Palumbo, an archaeologist with the University College London. It "contains high quantities of salts and is incompatible (being too strong and rigid) with traditional lime-based mortars." In China, restorers successfully used sticky rice-lime mortars to mend ancient structures, such as the single-arch Shouchang Bridge from the Song dynasty.

One group of conservationists is combining the timeworn technology of sticky rice with relatively new nanotechnology to develop an innovative treatment for historical sites. "This is an original and ecologic application that can be used to repair any lime-based structure, such as limestone or a lime mortar," says Jorge Otero, a researcher with the Getty Conservation Institute. His team is still testing the durability of their materials, but the capabilities of the ancient grain are evident. Soon, glutinous rice may glue together historical buildings around the world.

https://wb.md/2VfuWNt

Medical Cannabis Safe, Effective for Neurologic Symptoms in the Elderly

Medical cannabis may be safe and effective in the treatment of a wide range of chronic symptoms related to various neurologic illnesses in elderly patients, early research suggests.

Caroline Cassels

PHILADELPHIA — In a preliminary study, investigators at the Dent Neurologic Institute in Buffalo, New York, found that the drug provided elderly patients relief from chronic pain, sleep disorders, and anxiety related to diseases such as amyotrophic lateral sclerosis, Parkinson disease, neuropathy, spinal cord damage, and multiple sclerosis.

"Our findings show that medical marijuana is well-tolerated in people age 75 and older and may improve symptoms like chronic pain and anxiety," study investigator Laszlo Mechtler, MD, said in a release. "With legalization in many states, medical marijuana has become a popular treatment option among people with chronic diseases and disorders, yet there is limited research, especially in older people," he added. The findings were presented here at the American Academy of Neurology (AAN) 2019 Annual Meeting.

Promising Findings

Estimates from the Centers for Disease Control and Prevention show that approximately 80% of older adults in the United States have at least one chronic condition. In addition, it is estimated that 2.1 million Americans use medical cannabis.

To evaluate the efficacy and adverse events of medical cannabis in an elderly population, the investigators conducted a retrospective chart review of patients aged 75 years or older who were attending a neurologic outpatient clinic.

The study included 204 patients (129 women and 75 men) enrolled in New York State's Medical Marijuana Program. The average age of the participants was 81. The patients took tetrahydrocannabinol (THC) and cannabidiol (CBD), the main active ingredients in cannabis, in various ratios for an average of 4 months and had regular follow-up visits.

Medical cannabis was taken by mouth as a liquid extract tincture, capsule, or via an electronic vaporizer.

Results of the retrospective study showed that 69% of participants experienced some symptom relief. The most common conditions that improved were pain, for which 49% of patients experienced relief; sleep symptoms, for which 18% experienced relief; neuropathy, for which 15% experienced improvement; and anxiety, for which 10% experienced relief.

Initially, 34% of the cohort experienced side effects. However, after adjusting the dose, only 21% reported side effects. The most common side effects were sleepiness (13%), balance problems (7%), and gastrointestinal disturbances (7%). Three percent discontinued use because of adverse events. Interestingly, the results showed a decrease in opioid use in 32% of participants.

"Our findings are promising and can help fuel further research into medical marijuana as an additional option for this group of people who often have chronic conditions," the investigators note.

Limitations of the study were its retrospective design and its reliance on self-report with respect to symptom relief. Additional randomized, placebo-controlled studies are needed, said Mechtler.

"Future research should focus on symptoms like sleepiness and balance problems, as well as efficacy and optimal dosing," he said.

Rapid Uptick in the Elderly

Commenting on the findings for *Medscape Medical News*, Mark Wallace, MD, professor of clinical anesthesiology and chief of the Division of Pain Medicine, University of California, San Diego, who has extensive experience researching and treating pain patients with medical cannabis, said the study is unique in that it involved a geriatric population.

He noted that in his clinical practice, geriatric patients are the fastest growing group of medical cannabis users.

This rapid uptick of use among the elderly is not surprising, he said. "These patients are looking for alternatives. The medications we currently have on the market [for the treatment of neuropathic pain] probably reduce pain by no more than 30% in no more than 50% of the patients — that's pretty low."

In addition, he said, there is very limited evidence to support the long-term use of opioids, and in view of the current opioid crisis, many patients want to get off these medications.

Because cannabis is a Schedule 1 substance, no head-to-head studies have compared it to other currently available agents for chronic pain, so "these types of retrospective studies are actually very important," Wallace said.

The study's finding that cannabis may help reduce chronic opioid use, he added, mirrors the clinical experience at his center.

Reduced Opioid Use

"These patients come to me on high-dose opioids, and we are able to get them off opioids [by using medical cannabis]," he said.

"Patients who are taking high-dose opioids are constantly looking at the clock, waiting for the time when they can take their next dose, and are constantly monitoring their supply. When supply goes down, anxiety goes up. It completely controls their life. But when you put them on medical cannabis, that behavior completely goes away and they feel they have their lives back," Wallace added.

Determining the ratio of CBD to THC is a challenge and requires an individualized approach. However, said Wallace, for daytime use, it appears that a CBD-to-THC ratio of 20:1 may be best. At night, a 1:1 ratio appears most effective.

"Even in patients where [medical cannabis] doesn't help their pain, many — I would say upwards of 80% — opt to stay on it because it helps their sleep," he said.

It is important to note that medical cannabis is administered in very small doses — typically starting at a range of about 1 mg to 2 mg — and is very different from the cannabis that is used recreationally. "The doses that are being marketed on the recreational side have no place on the medical side. It is way too much and can actually

worsen the patient's pain, worsen sleep, and can cause agitation and paranoia," he said.

There is a misperception that treating elderly patients with medical cannabis may be unsafe and increase the risk for falls due to dizziness or cognitive impairment. However, Wallace said, the clinical experience at his center suggests this is not the case.

"We are finding that the geriatric population can successfully use medical cannabis without any adverse effects. I am having a lot of success with geriatric patients. It is amazing that even patients in their 90s are using it successfully," he said.

The study was supported by the Dent Family Foundation. Mechtler and Wallace report no relevant financial relationships.

American Academy of Neurology (AAN) 2019 Annual Meeting: Abstract P4.1-014. Presented May 8, 2019.

https://wb.md/2Jfi4Fx

Heart Meds May Prevent Vascular Dementia After Stroke

Two drugs for heart disease and angina — cilostazol (Pletal, Otsuka) and isosorbide mononitrate (ISMN) (multiple brands) — have neuroprotective potential for patients with lacunar ischemic stroke, new research suggests.

Megan Brooks

Results of the phase 2 LACunar Intervention-1 (LACI-1) trial show that cilostazol and ISMN are well tolerated individually and together in patients with lacunar stroke as an add-on to conventional secondary stroke prevention and may improve vascular function and cognition.

The results were published online April 23 in *EClinicalMedicine*.

Synergistic Effect?

Lacunar stroke is a frequent clinical manifestation of small vessel disease, the most common cause of vascular dementia.

"Patients have a high risk of recurrent stroke and also of cognitive decline after lacunar stroke. There are no established treatments to prevent or treat small vessel disease," study investigator Joanna M. Wardlaw, MBChB(Hons), MD, of University of Edinburgh, United Kingdom, told *Medscape Medical News*.

Cilostazol and ISMN have "promising modes of action" to prevent progression of small vessel disease, including relaxing small blood vessels and reducing inflammation, she added.

In studies conducted in Asia-Pacific countries, cilostazol has been shown to reduce recurrent stroke and incident dementia.

However, there is little experience with cilostazol in the treatment of lacunar stroke outside the Asia-Pacific region, nor is there experience with ISMN in the treatment of lacunar stroke anywhere, or of the drugs in combination, yet the effects are potentially synergistic.

"The purpose of LACI-1 was to see if patients with small vessel disease could take the drugs, to get some evidence for safety and efficacy, and to lay the infrastructure for larger trials," said Wardlaw.

The phase 2a, dose-escalation, prospective, randomized, open-label trial was conducted at two large stroke centers in the United Kingdom.

In the trial, 39 men and 18 women (mean age, 66 years) with clinically confirmed lacunar ischemic stroke who were without cognitive impairment were randomly allocated to receive ISMN 25 mg twice daily; cilostazol 100 mg twice daily; both ISMN and cilostazol, started immediately; or both drugs, started after a delay. Doses were escalated to target over 2 weeks and were sustained for 8 weeks.

Most patients (64%) achieved the full target dose by the end of the treatment period (the primary outcome). There was no difference between cilostazol vs ISMN and single vs dual drugs.

There were no drug-related adverse events or bleeding complications, despite the fact that all participants also took prescribed antiplatelet drugs.

In addition, the trial showed that both drugs affect systemic hemodynamic function and may improve vasoreactivity in white matter, reduce white matter lesions, and improve cognitive performance. All of these secondary outcomes "require confirmation in larger trials," the researchers note.

LACI-1 also demonstrates that the drugs are safe for use in lacunar stroke patients, taken alone or in combination, and supports further testing in larger trials with clinical endpoints, they say.

LACI-2, which aims to enroll 400 patients with lacunar stroke and is funded by the British Heart Foundation, is underway.

In LACI-2, patients with lacunar stroke will be treated with cilostazol and ISMN, alone or in combination, for a year to test the effects on recurrent stroke, cognition, tolerability, and safety.

"It is too early to say if the drugs will prevent progression of small vessel disease or recurrent lacunar stroke or cognitive decline, but LACI-2 will help," said Wardlaw.

Potential Breakthrough?

"There hasn't been a new drug for dementia for 15 years, so finding evidence that these cheap existing drugs could prevent dementia after a stroke would be a huge breakthrough," James Pickett, PhD, head of research at the Alzheimer's Society, said in a news release.

"It's promising to see that these two drugs are safe to use, and we'll be excited to see the results of the next stage of testing in a couple of years, which will show whether these drugs can be an effective treatment," added Pickett.

LACI-1 was funded primarily by the Alzheimer's Society, with support from the UK Stroke Association, the British Heart Foundation, the European Union, the National Institutes of Health Research, and National Health Service Research Scotland. The authors have disclosed no relevant financial relationships.

EClinicalMedicine. Published online April 23, 2019. Full text

http://bit.ly/2VqPfMJ

6 in 10 Infectious Diseases Come from Animals. The CDC Is Most Worried About These 8.

More than half of the infectious diseases that affect people come from animals. Now, for the first time, the government is releasing a list of the top eight illnesses spread from animals — called zoonotic diseases — in the United States.

By Yasemin Saplakoglu, Staff Writer | May 7, 2019 06:50am ET

The list includes some strains of the flu, *Salmonella* infection, West Nile virus, the plague, emerging coronaviruses such as Middle East respiratory syndrome, rabies, brucellosis (a bacterial infection) and Lyme disease, according to the list, released May 6 by the Centers for Disease Control and Prevention (CDC).

Experts from the CDC, along with experts from the U.S. Department of Agriculture and the Department of the Interior, came up with the list during a workshop held last December in Washington, D.C.

The eight illnesses were chosen based on the potential for the disease to cause an epidemic or pandemic, the severity of the disease, the economic impact, the potential for the introduction or spread of the disease in the U.S., and the potential for bioterrorism. (An epidemic refers to when a disease affects more of a given population than expected; a pandemic refers to a worldwide epidemic.)

Take the flu, for example. The flu can sicken many different animals, including cats, dogs and bats. And though certain strains of the virus are typically contained within certain species, the strains change all the time. In rare cases, the virus can mutate in a way that allows it to hop from whichever animal it usually infects to humans, and from there, spread to other humans.

Flu pandemics typically happen as a result of this hop from animals to humans, Live Science reported in March. For example, the 2009

flu pandemic — the swine flu — came from pigs. And the 1918 flu pandemic, which killed millions of people around the world, originated in birds.

Other zoonotic illnesses on the list include salmonellosis, caused by *Salmonella* bacteria, which leads to about 1.2 million illnesses every year in the U.S., according to the CDC. People can become infected by this bacterium if they eat food contaminated with the bacteria. Also on the list is a very rare, yet very serious zoonotic infection known as rabies, which is caused by a virus that can spread from animal bites.

The list also includes the West Nile virus, which can be transmitted from mosquitoes, and Lyme disease, an illness that comes from the bite of infected ticks. The plague (yes, it still exists) can be transferred to humans who have handled animals infected with the bacterium *Yersinia pestis*. The plague, unlike in the Middle Ages, is now treatable with antibiotics. Even so, the report concluded that one form of the plague — the deadly pneumonic plague — has the potential to spread until it's an epidemic, and the bacteria could also be used as a bioterrorism agent.

http://bit.ly/2JcxV7K

Why Mathematicians Are Obsessed with (and Hoarding) This Chalk

By Mindy Weisberger, Senior Writer | May 7, 2019 07:07am ET

A type of blackboard chalk that was produced for decades by just one factory in Japan was so highly prized by mathematicians they referred to it as "the Rolls-Royce of chalk."

And when rumors surfaced about the chalk being discontinued, some academics resorted to stockpiling as many boxes as they could get their chalk-covered hands on.

The tale of Fulltouch chalk, manufactured by Hagoromo Stationery in Nagoya, Japan, and thought by many to be the finest chalk in the world, was recently featured in a short video, shared on YouTube on May 2 by Great Big Story.

Hagoromo made chalk for more than 80 years, and for those who weren't lucky enough to live in Japan, Fulltouch was always difficult to get. Then, as Hagoromo prepared to shut down in 2015, many dedicated aficionados began grimly preparing for a world without Fulltouch. They bought dozens upon dozens of boxes, some hoarding enough chalk to last through the end of their careers, according to the video.

When Fulltouch production ended, it triggered a "chalkapocalypse" for mathematicians. **Great Big Story/YouTube**

What is so special about this chalk? Mathematicians in the video described Fulltouch in glowing terms. The chalk is long-lasting, virtually unbreakable, bright and easy to read on a chalkboard, smooth as butter to write with, and practically dustless, Jeremy Kun, a Google engineer with a Ph.D. in mathematics, wrote in a 2015 blog post bidding farewell to Fulltouch.

So renowned is the chalk among mathematics professionals that it is accompanied by its own legend: It is impossible to write a false theorem with it, David Eisenbud, director of the Mathematical Sciences Research Institute in Oakland, California, said in the video.

When the news broke that Fulltouch's maker was ceasing production and closing its doors, it launched a "chalkapocalypse" among mathematicians, said Brian Conrad, a professor at Stanford University in California. In the video, Conrad and others recounted their responses to the chalk emergency, stocking up on enough to carry them through as much as 15 years in a chalk desert.

However, there is a ray of hope for those who didn't have the foresight to fill their closets and cupboards with Fulltouch when they had the chance. Hagoromo sold the Fulltouch recipe — and

two of the factory's original chalk-making machines — to the Korean company Sejongmall. The chalk is being manufactured again under its original name, and is available to buy in the U.S. on Amazon.

http://bit.ly/2VQtVzN

Ensuring oral medicines are protected from the acidic conditions of the stomach

A group of chemical and biomedical engineers at UNSW Sydney and University of Cambridge has improved the chemical stability of 'ZIF crystals', enabling these porous nanomaterials to be used for smart pharmaceutical drug delivery in the human body.

by Lachlan Gilbert, University of New South Wales

ZIF crystals – an abbreviation of zeolitic imidazolate frameworks – have been used as an exoskeleton shell for a wide range of pharmaceuticals, from small anti-cancer drugs to large proteins and enzymes. What has made these organic and metallic hybrid compounds so attractive to biochemical engineers is the potential to target specific diseases or locations in the body to maximise the therapeutic effect while greatly reducing side effects.

But up until now, the effectiveness of the material to protect the drugs they are transporting has been compromised by their instability once exposed to acidic conditions within the body – such as in the stomach, when taken orally.

UNSW chemical engineer and Scientia Fellow Kang Liang says ZIF crystals show great potential as the next generation technology for personalised medicine, so there has been considerable interest in fixing this flaw. Luckily, he and his colleagues have done just that.

"We managed to incorporate soft biomolecules like DNA, polypeptides and enzymes to improve the stability of the rigid ZIF crystals," he says. "Before this we had the problem where the ZIF crystal exoskeleton would degrade and the drugs would leak out before they reached the target – rendering the drug ineffective."

"Our discovery shows that we can potentially encapsulate the therapeutic molecules that we want to deliver to the body inside ZIF crystals. Surprisingly these therapeutic molecules can stabilise the ZIF crystals, while at the same time, the ZIF crystals protect the therapeutics before they reach the target site. So there is a mutual benefit."

It is not just medicine that will benefit from the researchers' advances in stabilising ZIF crystals. ZIF crystals also have applications as electrode materials in supercapacitors, as a carbon dioxide capture material in untreated gas flue systems, as a molecular separation membrane for water treatment and in ionic sieving.

"The concept of composite bonding that we demonstrated in ZIF crystals is a hot area for theoretical investigation and engineering research," says co-author Dr. Jingwei Hou, who worked in UNSW's School of Chemical Engineering before joining Cambridge University.

He adds that the group will be looking next to combining AI and machine learning methods with their research to potentially expand the new knowledge to include a larger range of soft molecules and porous crystals. The group's work was published today in *Chem*.

More information: *Improving the Acidic Stability of Zeolitic Imidazolate Frameworks by Biofunctional Molecules. Chem.* *doi.org/10.1016/j.chempr.2019.03.025*

http://bit.ly/2vSi6dS

Why visual stimulation may work against Alzheimer's

New findings help explain the surprising discovery that exposure to flickering light reduces amyloid plaques in mice

CAMBRIDGE, MA -- Several years ago, MIT neuroscientists showed that they could dramatically reduce the amyloid plaques seen Alzheimer's disease in mice simply by exposing the animals to light flickering at a specific frequency.

In a new study, the researchers have found that this treatment has widespread effects at the cellular level, and it helps not just neurons but also immune cells called microglia. Overall, these effects reduce inflammation, enhance synaptic function, and protect against cell death, in mice that are genetically programmed to develop Alzheimer's disease.

"It seems that neurodegeneration is largely prevented," says Li-Huei Tsai, the director of MIT's Picower Institute for Learning and Memory and the senior author of the study.

The researchers also found that the flickering light boosted cognitive function in the mice, which performed much better on tests of spatial memory than untreated mice did. The treatment also produced beneficial effects on spatial memory in older, healthy mice. Chinnakkaruppan Adaikkan, an MIT postdoc, is the lead author of the study, which appears online in Neuron on May 7.

Beneficial brain waves

Tsai's original study on the effects of flickering light showed that visual stimulation at a frequency of 40 hertz (cycles per second) induces brain waves known as gamma oscillations in the visual cortex. These brain waves are believed to contribute to normal brain functions such as attention and memory, and previous studies have suggested that they are impaired in Alzheimer's patients.

Tsai and her colleagues later found that combining the flickering light with sound stimuli -- 40-hertz tones -- reduced plaques even further and also had farther-reaching effects, extending to the hippocampus and parts of the prefrontal cortex. The researchers have also found cognitive benefits from both the light- and sound-induced gamma oscillations.

In their new study, the researchers wanted to delve deeper into how these beneficial effects arise. They focused on two different strains of mice that are genetically programmed to develop Alzheimer's symptoms. One, known as Tau P301S, has a mutated version of the Tau protein, which forms neurofibrillary tangles like those seen in Alzheimer's patients. The other, known as CK-p25, can be induced to produce a protein called p25, which causes severe neurodegeneration. Both of these models show much greater neuron loss than the model they used for the original light flickering study, Tsai says.

The researchers found that visual stimulation, given one hour a day for three to six weeks, had dramatic effects on neuron degeneration. They started the treatments shortly before degeneration would have been expected to begin, in both types of Alzheimer's models. After three weeks of treatment, Tau P301S mice showed no neuronal degeneration, while the untreated Tau P301S mice had lost 15 to 20 percent of their neurons. Neurodegeneration was also prevented in the CK-p25 mice, which were treated for six weeks.

"I have been working with p25 protein for over 20 years, and I know this is a very neurotoxic protein. We found that the p25 transgene expression levels are exactly the same in treated and untreated mice, but there is no neurodegeneration in the treated mice," Tsai says. "I haven't seen anything like that. It's very shocking."

The researchers also found that the treated mice performed better in a test of spatial memory called the Morris water maze. Intriguingly, they also found that the treatment improved performance in older mice that did not have a predisposition for Alzheimer's disease, but not young, healthy mice.

Genetic changes

To try to figure out what was happening at a cellular level, the researchers analyzed the changes in gene expression that occurred in treated and untreated mice, in both neurons and microglia -- immune cells that are responsible for clearing debris from the brain.

In the neurons of untreated mice, the researchers saw a drop in the expression of genes associated with DNA repair, synaptic function,

and a cellular process called vesicle trafficking, which is important for synapses to function correctly. However, the treated mice showed much higher expression of those genes than the untreated mice. The researchers also found higher numbers of synapses in the treated mice, as well as a greater degree of coherence (a measure of brain wave synchrony between different parts of the brain).

In their analysis of microglia, the researchers found that cells in untreated mice turned up their expression of inflammation-promoting genes, but the treated mice showed a striking decrease in those genes, along with a boost of genes associated with motility. This suggests that in the treated mice, microglia may be doing a better job of fighting off inflammation and clearing out molecules that could lead to the formation of amyloid plaques and neurofibrillary tangles, the researchers say. They also found lower levels of the version of the Tau protein that tends to form tangles.

A key unanswered question, which the researchers are now investigating, is how gamma oscillations trigger all of these protective measures, Tsai says.

"A lot of people have been asking me whether the microglia are the most important cell type in this beneficial effect, but to be honest, we really don't know," she says. "After all, oscillations are initiated by neurons, and I still like to think that they are the master regulators. I think the oscillation itself must trigger some intracellular events, right inside neurons, and somehow they are protected."

The researchers also plan to test the treatment in mice with more advanced symptoms, to see if neuronal degeneration can be reversed after it begins. They have also begun phase 1 clinical trials of light and sound stimulation in human patients.

The research was funded by the National Institutes of Health, the Halis Family Foundation, the JPB Foundation, and the Robert A. and Renee E. Belfer Family Foundation.

http://bit.ly/309bQw0

Sunscreen Ingredients Absorbed into Blood: Study

FDA researchers report that multiple active ingredients wind up in users' bloodstream and recommend toxicology testing to investigate the clinical significance of the findings.

Catherine Offord

Several active ingredients of sunscreen can be detected at high concentrations in the blood after just one day of frequent use, according to the results of a small clinical trial by the US Food and Drug Administration published yesterday (May 6) in *JAMA*. The results do not indicate that the ingredients cause any harm, say researchers, but do provide justification for further investigation of their potential toxicities.

"It's not news that things that you put on your skin are absorbed into the body," Scott Faber, senior vice president for government affairs at the health advocacy organization the Environmental Working Group, tells *CNN*. Faber, who was not involved in the work, adds that "this study is the FDA's [Food and Drug Administration's] way of showing sunscreen manufacturers they need to do the studies to see if chemical absorption poses health risks."

To conduct the study, the researchers collected blood samples from 24 healthy volunteers, who applied one of four sunscreens over 75 percent of their skin, four times a day, for four days.

The team found that four active ingredients—avobenzone, oxybenzone, octocrylene, and ecamsule—were all absorbed into the blood, although their concentrations varied by product. Average concentrations of avobenzone, for example, ranged from 1.8 ng/mL up to 4.3 ng/mL.

Earlier this year, the FDA proposed a new rule for over-the-counter sunscreen products that would stipulate that any active ingredient absorbed into the blood with concentrations greater than 0.5 ng/mL

undergo toxicology testing. All four ingredients measured in this study exceeded that threshold after just one day of use.

Little is known about the toxicities of these ingredients, although some research has linked oxybenzone—which was detected at concentrations of more than 200 ng/mL for one of the products tested—to hormone changes in men and boys.

Further investigation into such effects is warranted, Kanade Shinkai, a dermatologist at the University of California, San Francisco, and the editor-in-chief of *JAMA Dermatology*, tells *Wired*. "There might be nothing, and that would be great," she says. "But the problem is that we just don't know."

In the meantime, researchers recommend that people keep using sunscreen. "These products are used to prevent skin cancer," study coauthor Theresa Michele, director of the FDA's division of nonprescription drug products, tells *NBC*. "It's very important from a public health perspective that people use them, especially as skin cancer rates are increasing. Right now, we know that there are benefits from these products and we don't know if there are any harms."

http://bit.ly/2HfiaL2

Experimental cosmologist group launches its first iterations of space-traveling 'wafercraft'

Laser-propelled to relativistic speeds to reach nearby star systems

by Sonia Fernandez

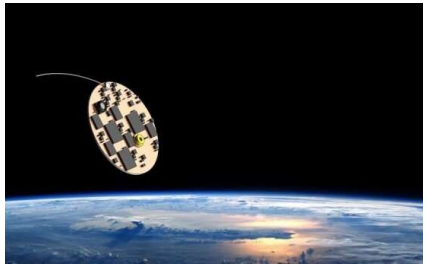
UC Santa Barbara students sent up, via balloon, a prototype miniature spacecraft that might eventually become the "wafercraft" that researchers posit could be propelled by lasers to achieve space travel at relativistic speeds to reach nearby star systems and exoplanets.

So begins a journey, funded by NASA and several private foundations, that may one day lead to interstellar travel.

"It's part of a process of building for the future, and along the way you test each part of the system to refine it," said UC Santa Barbara physics professor and experimental cosmologist Philip Lubin. "It's part of a long-term program to develop miniature spacecraft for interplanetary and eventually for interstellar flight."

The prototype wafer scale spacecraft (WSS) is small enough to fit in the palm of one hand. It was launched into the stratosphere above Pennsylvania, to an altitude of 105,000 feet (32 km)—three times that of commercial airplanes—to gauge its functionality and performance.

The launch was conducted in collaboration with the United States Naval Academy in Annapolis on April 12, 2019—58 years to the day that Russian cosmonaut and pilot Yuri Gagarin became the first human to complete orbital space flight.



These are the adventures of the "StarChip Wafersize." **Credit: University of California - Santa Barbara**

"It was designed to have many of the functions of much larger spacecraft, such as imaging, data transmission, including laser communications, attitude determination and magnetic field sensing," said Nic Rupert, a development engineer in Lubin's lab. "Due to the rapid advancements in microelectronics we can shrink a spacecraft into a much smaller format than has been done before for specialized applications such as ours."

The spacecraft prototype worked flawlessly and collected more than 4000 images of the Earth in what Rupert said was "an excellent first flight and it will evolve dramatically from here."

The project's goal, as the device's name suggests, is to build an ultra-lightweight (gram scale) silicon wafer with embedded electronics, capable of being shot into space while relaying data

back to Earth. For the distance the researchers want to achieve—roughly 25 trillion miles, or 40 trillion kilometers, cruising at a significant fraction of the speed of light—the technology required is daunting.

"Ordinary chemical propulsion, such as that which took us to the moon nearly 50 years ago to the day, would take nearly one hundred thousand years to get to the nearest star system, Alpha Centauri," Lubin said. "And even advanced propulsion such as ion engines would take many thousands of years. There is only one known technology that is able to reach the nearby stars within a human lifetime and that is using light itself as the propulsion system."

Known as directed energy propulsion, the technology requires building an extremely large array of lasers to act as the propulsion. This system does not travel with the spacecraft; it remains on Earth.

"If you have a large enough laser array, you can actually push the wafers with a laser sail to get to our goal of 20 percent of the speed of light," Rupert said. "Then you'd be at Alpha Centauri in something like 20 years."

Part of a NASA-funded endeavor called Starlight, the effort is supported also by the Breakthrough Foundation, where it is known as Starshot. UC Santa Barbara initiated the project in 2009 with modest funding from NASA's Spacegrant program, receiving additional funds in 2015 via NASA Advanced Concepts.

The UC Santa Barbara team then approached billionaire tech investor Yuri Milner's Breakthrough Foundation in 2016 to share the implications of the technology. In April of that same year, the foundation announced it would undertake a $100 million effort to back this program.

The purpose is to answer one of humanity's biggest existential questions: Are we alone in the universe? And one way to find out, according to the researchers, is to visit nearby exoplanets by sending a multitude of these tiny spacecraft to nearby star systems. These chips would contain nanoscale cameras, navigation equipment, communications technology and other systems to search nearby exoplanets far beyond our solar system for evidence of life.

Still another facet of the UC Santa Barbara project involves sending life from Earth into space. The researchers want to to test the idea of transporting life over vast distances using radiation-hardened, cryo sleep-capable, space-hardy tiny animals—specifically, tardigrades and the nematode c. elegans.

But first, the technology has to exist. Thanks to advances in photonics and silicon electronics, seeds of the final products have been planted, say the scientists. Repeated attempts to send the evolving hardware into ever-farther reaches of our atmosphere, and gradually into outer space and beyond, are what they hope will seal the deal.

"The point of building these things is to know what we want to include in the next version, in the next chip," said David Mc Carthy, a graduate student in the Department of Electrical and Computer Engineering. "You start with off-the-shelf components because you can iterate quickly and inexpensively." At this stage, he said, the idea is to see how well the hardware works under increasingly harsh conditions, including freezing temperatures, extended exposure to radiation such as cosmic rays and collisions with particles between Earth and the stars (the interstellar medium), and the hard vacuum of space.

The momentum is building. An interdisciplinary undergraduate group, consisting of students from physics, engineering, chemistry and biology, are conducting balloon flights to gather data that may eventually inform the development of future versions of the wafercraft. As the technology becomes increasingly sophisticated, the researchers said, they can engage the semiconductor industry to turn out these tiny spacechips in bulk at low cost.

Meanwhile, innovations in silicon optics and integrated wafer-scale photonics are making it possible to reduce the costs of the laser array used for launching these spacecraft. Faculty and researchers in UC Santa Barbara's electrical and computer engineering department are playing a critical role.

"It's not that unrealistic to think that we can make one-gram pieces of silicon that are going to have everything we want on them," Mc Carthy said.

Ultimately shooting for interstellar space, which is still quite a way off, the group is aiming for a suborbital first flight next year. The development of such technology paves the way toward a variety of space missions that would have been considered too costly or impossible with conventional chemical rocket-powered technology.

Potential benefits of the core technology? Much shorter trip times to Mars than is currently possible; planetary defense against asteroids and comets; mitigating space debris, boosting Earth-orbiting satellites, or remotely powering distant solar system outposts, among many others, noted Lubin.

"It enables a whole class of technological abilities," he said, of directed energy propulsion. "Some of the more interesting, short-term ones would involve interplanetary missions."

The UCSB group has published over technical 50 papers on the transformational technology they are developing and the radical implications it has for human exploration.

https://nyti.ms/2vQQGFb

Dinosaur With Bat Wings Was More Than Legend

Chinese scientists first thought it was a prehistoric bird, until chipping away at the fossil revealed surprising features.

By Lucas Joel

Imagine an animal that looks like a dinosaur, and you probably will not imagine a bat. But that may change. A team of paleontologists in China announced on Wednesday the discovery of a dinosaur that sported the same kinds of fleshy wings bats use to flit through the air.

The dinosaur, Ambopteryx longibrachium, lived about 163 million years ago. When Min Wang, a vertebrate paleontologist at the Chinese Academy of Sciences, first saw the fossil, which he and his team pulled out of Jurassic-age rocks in Liaoning Province in China, "I thought it was a bird," he said.

Ambopteryx longibrachium, a newly discovered species of scansoriopterygid dinosaur with bat-like wings, found in Liaoning Province, China. **Min Wang/Chinese Academy of Sciences**

Birds evolved from dinosaurs, and so the two groups share many features. Dr. Wang assumed Ambopteryx was a bird because the animal sported relatively long forelimbs, just as modern birds do. But as his team carefully chipped away the rock surrounding the fossil over the course of about a year, distinctly dinosaurian features began to emerge. Ambopteryx, for one thing, had long fingers, a trait that birds lack.

Dr. Wang's team was also surprised to find the remains of soft tissue around the dinosaur's arms and torso. This tissue, in life, formed flaps of skin that probably resembled batlike wings, Dr. Wang said.

The new find, published in the journal Nature, follows a report in Nature in 2015 — by a team including authors of the new paper — that described the only other known batlike dinosaur. That animal, called Yi qi, was the first of its kind, and other paleontologists were skeptical. The doubts arose because Yi qi was so bizarre.

"I think that if you had asked a paleontologist to just draw up some kind of fantasy dinosaur, you know, a lot of us never would have come up with something that was that weird," said Stephen

Brusatte, a vertebrate paleontologist at the University of Edinburgh, who was not involved in the new research. But the discovery of Ambopteryx, which is a close cousin of Yi qi, “pretty much seals the deal that there was this group of dinosaurs with batlike wings,” he said.

So batlike dinosaurs definitely existed. But exactly how Ambopteryx flew through the air remains unclear. The team’s best guess is that the animal’s flying style was “halfway between a flying squirrel and a bat,” said Jingmai O’Connor, a co-author and a vertebrate paleontologist at the Chinese Academy of Sciences.

Despite this lingering mystery, Dr. Brusatte said, the discovery of Ambopteryx underscores that on the dinosaur family tree, there were several branches — not just the one that led to birds — that gave rise to flying dinosaurs. And, he added, it is unsurprising that dinosaurs may have evolved to fill the kinds of ecological roles filled today by mammals such as flying squirrels.

Perhaps paleontologists should not be too shocked by the next oddity they dig up.

“Maybe a dinosaur with seven arms, or a tyrannosaur with a big horn sticking out of its head, or, I don’t know, a brachiosaurus with webbed feet,” he said. “I have no idea! Who knows what we might find. But that makes the field very, very exciting.”

http://bit.ly/2WDc64j

Appendix removal associated with development of Parkinson's disease

Data from 62 million records explores relationship between the gut and the nervous system disorder

San Diego, Calif. - Patients who had their appendix removed were more likely to develop Parkinson's disease than those whose appendix remained in place, according to the largest study to address the relationship between the two conditions. The retrospective study involving more than 62 million patient records from 26 health systems will be presented at Digestive Disease Week® (DDW) 2019.

"Recent research into the cause of Parkinson's has centered around alpha synuclein, a protein found in the gastrointestinal tract early in the onset of Parkinson's," said Mohammed Z. Sheriff, MD, lead author of the study and a physician at Case Western Reserve University and University Hospitals Cleveland Medical Center, Ohio. "This is why scientists around the world have been looking into the gastrointestinal tract, including the appendix, for evidence about the development of Parkinson's."

Previous findings on appendectomies and Parkinson's have been inconsistent, with some studies showing no relationship and a recent study from Europe showing patients who still had their appendix were more likely to develop Parkinson's. This contradiction prompted Dr. Sheriff and colleagues to seek answers to the question using U.S. data from an Ohio-based electronic health records company that draws data from 26 major integrated health systems.

Researchers analyzed electronic health records representing more than 62.2 million patients and identified those who had appendectomies and were diagnosed with Parkinson's disease at least six months later.

They found that among 488,190 patients who had undergone appendectomies, 4,470, or .92 percent, went on to develop Parkinson's. Of the remaining 61.7 million patients without appendectomies, they identified only 177,230, or .29 percent, who developed the disease. According to this analysis, patients who had an appendectomy were more than three times as likely to develop Parkinson's than those who had not.

Researchers found similar risk levels across all age groups, regardless of gender or race. Other than the six-month washout period programmed into their initial query of the database,

researchers could not tell from the de-identified records exactly how much time passed after the appendectomy until Parkinson's was diagnosed.

"This research shows a clear relationship between the appendix, or appendix removal, and Parkinson's disease, but it is only an association," Dr. Sheriff said. "Additional research is needed to confirm this connection and to better understand the mechanisms involved."

https://go.nature.com/2vRzsY3

Long-extinct pandas left a living legacy

Giant pandas were once far more widespread — and more genetically diverse — than they are today.

A panda that vanished from Asia thousands of years ago survives in the genome of its modern relatives.

The giant panda (*Ailuropoda melanoleuca)* once thrived as far north as Beijing and as far south as Vietnam, but today the bear lives in only six mountain ranges in central China. To study the effects on the species of its shrinking territory, Gui-Lian Sheng at the China University of Geosciences in Wuhan, Axel Barlow at the University of Potsdam in Germany and their colleagues sequenced nuclear DNA from an approximately 5,000-year-old panda bone found in Yunnan Province, China, which lies well south of the animal's current habitat.

The giant panda's family tree includes an extinct ancestor that lived well south of the species' current range. **Eric Baccega/NPL**

Analysis indicated that the ancient bone came from a member of a now-vanished group of giant pandas. But DNA analysis also suggested that animals from this extinct lineage interbred with the ancestors of modern pandas millennia ago. The findings imply that giant pandas were more genetically diverse before their range shrank in size. *Curr. Biol.* (2019)

http://bit.ly/2Hh7ICY

Scientists locate brain area where value decisions are made

Data from mouse neurons point to unexpected brain region, carrying implications for health and disease

Neurobiologists at the University of California San Diego have pinpointed the brain area responsible for value decisions that are made based on past experiences.

Senior author Takaki Komiyama says data from tens of thousands of neurons revealed an area of the brain called the retrosplenial cortex, or RSC, which was not previously known for "value-based decision-making," a fundamental animal behavior that is impaired in neurological conditions ranging from schizophrenia to dementia and addiction.

Such decision-making is not the kind we encounter, for example, when navigating traffic lights, which are external cues that dictate our car-driving decisions. Rather, Komiyama, lead author Ryoma Hattori and their colleagues found that the RSC is the home region for decisions such as where we buy our morning coffee. When we visit a coffee shop, our subjective value of the shop is updated based on our experience in the RSC where the value is maintained until the next time we go out for coffee.

The research is published May 9 in the journal *Cell*.

"When you have two coffee shops to choose from, no one is telling you which one to go to--you rely on the internal value in order to choose one over the other," said Komiyama, a neurosciences professor in UC San Diego's Division of Biological Sciences and School of Medicine, and a founding faculty member of the Halıcıoğlu Data Science Institute. "How the brain maintains this

value information--and how it might be different in healthy and disease states--could be relevant in clinical applications."

The research team simultaneously imaged more than 500 neurons across six brain regions in mice. The resulting data trove of more than 45,000 recordings allowed them to compare how value-related information is processed in each brain area. This vast data set led them to the RSC, an area in the outer layer of the cerebrum known as the cortex, which connects a range of brain networks and functions.

"We found that the RSC, which previously had not been studied in the context of value-based decision-making, showed the strongest value information most persistently over time. These were unique characteristics," said Komiyama.

To confirm whether the value information in RSC is used for decision making, the researchers inactivated the RSC using a technique called optogenetics, which uses light-activatable proteins to manipulate neural activity. Results showed that these mice did not remember what happened in previous experiences.

"Basically, we made the mice forget the recent history by inactivating this particular RSC area," said Hattori. The researchers are now studying how the RSC interacts with other brain systems to establish and maintain value-based activity patterns.

Komiyama, whose lab generates nearly a terabyte of data per day, says science's recent capacity to record and study massive data sets opens new windows to our understanding of basic neurological functions.

"Previously these types of experiments were with one neuron at a time, which was simple to analyze," said Komiyama. "Technological advances are allowing new experiments with thousands and thousands of recordings of neuronal activity that can be related to various features of behavior. I'm sure we're still just scratching the surface of these complex data so the next new challenge has become big data analysis."

Coauthors of the study in the Komiyama Laboratory included Bethanny Danskin, Zeljana Babic and Nicole Mlynaryk of UC San Diego's Division of Biological Sciences Section of Neurobiology, the Center for Neural Circuits and Behavior and the Department of Neurosciences, School of Medicine.

http://bit.ly/2E2U2ZX

North York General study shows safest method for prostate cancer biopsies

New study shows the benefits of transperineal prostate biopsies under local anesthetic

TORONTO - The Gale and Graham Wright Prostate Centre at North York General Hospital (NYGH) is advancing prostate cancer care with a new study that shows the benefits of transperineal prostate biopsies (TPBx) under local anesthetic.

Published online in the *Journal of Urology* the study, "Transperineal Prostate Biopsies Using Local Anesthesia: Experience in 1,287 Patients. Prostate Cancer Detection Rate, Complications and Patient Tolerability" provides evidence that the TPBx approach for testing and diagnosing prostate cancer is accurate and has significantly fewer complication rates compared to the traditional prostate biopsy method.

"After performing more than a thousand TPBx procedures under local anesthetic, the team at North York General has shown that it is the safest method of obtaining a biopsy for prostate cancer and patients tolerate the procedure well," said Dr. Stan Flax, NYGH urologist and one of the study's lead authors. "The clinical data provides the necessary evidence that the medical community needs in order to move toward a new standard of care for patients."

In 2016, NYGH's Gale and Graham Wright Prostate Centre became the first in Canada to use the TPBx approach, which involves obtaining the biopsy using a needle through the skin. Studies have shown that TPBx is a safer alternative for patients, as compared to

transrectal biopsies, due to the lower risk of serious infections, which can result in hospitalization and admission to an intensive care unit.

In the very few settings where TPBx is performed, the procedure is done using general or spinal anesthetic, which typically requires more intensive resources. For the past three years, urologists at NYGH have exclusively used TPBx under local anesthetic and have tracked a total of 1,287 procedures as part of this study. The data shows this method of prostate biopsies has the same accuracy rate, if not better as transrectal, compared to the team's previous series of transrectal biopsies.

Prostate cancer is the most commonly diagnosed cancer among North American men, with approximately one in seven men being diagnosed with this disease in their lifetime. It is also one of the more treatable cancers, if detected and treated in its early stages.

"Only one percent of testing for prostate cancer in North America is done using TPBx," says Dr. Flax. "Given how often prostate biopsies are performed, there is a real opportunity to improve patient care with our research."

http://bit.ly/2JkZOuz

Whole body MRI may help to detect spread of cancers more quickly

Largest trials of their kind suggest that whole body MRI may be quicker and cheaper than standard imaging for detecting spread of colorectal and non-small cell lung cancers, while just as sensitive

Trials with people with newly-diagnosed colorectal and non-small cell lung cancer suggest that whole body MRI could reduce the time it takes to diagnose the stage of cancers. The results are from two prospective trials with nearly 500 patients across 16 UK hospitals, published in *The Lancet Gastroenterology & Hepatology* and *The Lancet Respiratory Medicine* journals.

Whole body MRI scans reduced the average time to determine the size of tumours and how much they had spread by five days for colorectal cancer patients and six days for lung cancer patients. The treatments decided upon were similar, since results from MRI were as accurate as from standard investigations, but the costs per patient were reduced by nearly a quarter in the case of colorectal cancer and were almost halved for lung cancer. More research is needed to determine how this affects outcomes for patients.

Despite their accuracy and efficiency, the authors note that MRI scanners are not as widely available as other imaging technologies and are in high demand. In the trials, many of the hospitals were not able to find time on their MRI scanners, meaning that patients were examined in nearby hospitals.

"Our results, obtained in a real-world NHS setting, suggest that whole body MRI could be more suitable for routine clinical practice than the multiple imaging techniques recommended under current guidelines," says lead author Professor Stuart Taylor from UCL, UK. "While demands on NHS MRI scanners is currently high, MRI can image the whole body in one-hour or less Adopting whole body MRI more widely could save rather than increase costs, as well as reducing the time before a patient's treatment can begin." [1]

Appropriate treatment cannot be decided upon until the size of a tumour and the extent to which it has spread to nearby lymph nodes and other parts of the body has been determined. Standard NHS pathways often involve different imaging techniques - such as CT, PET-CT or focused MRI scans - which vary in accuracy in different organs. Several appointments and follow-up examinations can therefore be necessary.

For the first time, the two new trials compare the diagnostic accuracy and efficiency of whole body MRI with the standard NHS pathways, which use a range of imaging techniques for assessing colorectal and lung cancers. The standard imaging tests

recommended by the National Institute for Health and Care Excellence (NICE) [2] were undertaken as usual and the usual multi-disciplinary panel made a first treatment decision based on their results. Once this decision had been recorded, they considered images and reports from whole body MRI. If the latter highlighted a need for further tests, these were carried out. The panel were then able to say whether their first treatment decision would have different based on WB-MRI result. In the interests of patient care, the final decision was made based on results from all tests.

Patients were also followed up after 12 months to better evaluate the accuracy of whole body MRI compared with standard tests. For example, whether one approach was more sensitive than the other in detecting spread of the primary tumour to other parts of the body. Based on this data, the panel were able to retrospectively evaluate what the optimal treatment decision should have been.

Sensitivity and specificity of diagnosis for whole body MRI did not differ from standard tests for both cancers. The use of whole body MRI reduced the time it took to complete diagnostic tests, from an average of 13 days to an average of 8 days in the colorectal cancer trial and from 19 days to 13 days in the lung cancer trial. Costs were reduced from an average of £285 to £216 in the colorectal cancer trial and from an average of £620 to £317 in the lung cancer trial.

In the colorectal cancer trial, agreement with the final multi-disciplinary panel treatment decision based on standard investigations and whole body MRI was similar and high (95% and 96%, respectively), as were results for the lung cancer trial (99% for standard investigations, and 98% for whole body MRI).

Eight of the 16 hospitals in the colorectal cancer trial and 11 of the 16 hospitals in the lung cancer trial did not have the infrastructure to perform whole body MRI.

The authors note that their findings are specific to colorectal and non-small cell lung cancer and might not be relevant to tumours arising in other parts of the body. In addition, waiting times might not be representative of other UK hospitals or of hospitals in other countries. A further limitation of the lung cancer trial is that sensitivity in detecting the spread of cancers - including the development of secondary tumours and the spread to lymph nodes - was low using both current standard imaging techniques and whole body MRI. Further research is needed to improve the performance of non-invasive imaging.

Writing in a linked Comment, Professor Andreas Schreyer from Brandenburg Medical School, Germany, says of the colorectal cancer trial: "MRI has faced considerable backlash within the medical community due to relatively high costs and the problems involved in finding a timely slot for imaging because of the high demand for this method. This is why it is particularly important to think outside the box and look out for new medical pathways and paradigms and not to be driven by prejudices. It could be more efficient to adapt the known therapeutic concept of hitting hard and early to diagnostic imaging to improve medical outcomes and economic performance."

The trials were funded by the UK National Institute for Health Research.

[1] Quote direct from author and cannot be found in the text of the Article.

[2] For both lung and colorectal cancer, the UK National Institute for Health and Care Excellence (NICE) provides guidance on staging pathways:

In colorectal cancer, CT of the chest abdomen and pelvis is recommended, supplemented by pelvic MRI for local staging of rectal cancer. In routine clinical practice it is not unusual for patients to undergo PET CT and/or liver MRI if disease spread is suspected.

Staging pathways in lung cancer are more complex, with CT, PET-CT, MRI, US and endobronchial/ percutaneous biopsy all recommended at various points during staging.

http://www.thelancet.com/journals/langas/article/PIIS2468-1253(19)30056-1/fulltext and http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30090-6/fulltext

http://bit.ly/30fsnyA

A Dying Teenager's Recovery Started in the Dirt

One of the viruses used to treat her infections came from the side of a rotting South African eggplant.

Ed Yong

In 2010, when Lilli Holst scraped a lump of soil from the underside of a rotting eggplant, she had no idea that this act would help to save the life of a British teenager, eight years later and 6,000 miles away.

Holst, an undergraduate at the University of KwaZulu-Natal, in South Africa, was participating in a project in which students search through local soil samples for new phages—viruses that infect and kill bacteria. Holst found several, and gave them all names. In a worm farm, she discovered Liefie. In an aloe garden, Lixy. And from that decaying eggplant, Muddy. All three viruses infect a common bacterium called *Mycobacterium smegmatis*. And all of them were new to science.

Samples of Muddy and the other phage viruses made their way to the lab of Graham Hatfull, a phage expert at the University of Pittsburgh. He stored them in a freezer, along with at least 10,000 others that had also been discovered and named by students: Mariokart, TGIPhriday, Chupacabra, Benvolio, ChickenNugget, IAmGroot, and more. They were sitting there, in the cold, when in late 2017 Hatfull got a call from doctors at Great Ormond Street Hospital, in London.

The London team, led by the pediatrician Helen Spencer, had been treating a 15-year-old girl with cystic fibrosis—a genetic disorder that leads to persistent lung infections. To prepare for a double lung transplant, the girl had been taking drugs to suppress her immune system, and these allowed an already present microbe called *Mycobacterium abscessus* to run amok through her body. She had new lungs, but also heavy infections in her liver, limbs, buttocks, and torso, and in the surgical wound on her chest. Antibiotics weren't working, and the outlook was grim. The team put her on a palliative-care plan.

But Hatfull has spent decades studying phages that attack mycobacteria, the group to which the girl's life-threatening microbes belonged. Her doctors wanted to know whether he had anything in his arsenal that might kill those particular strains. He looked in his database—and found Muddy.

In laboratory tests, Muddy efficiently destroyed the exact strain of *M. abscessus* that was itself destroying the London patient's body. "It was good that we found one," Hatfull says. "But it was bad that we only found one," because bacteria can easily evolve to resist any single phage.

His team eventually found two more phages— BPs and ZoeJ—that had the potential to kill *M. abscessus*, but weren't doing it very well. Some phages kill the bacteria they infect by reproducing frantically and bursting out in fatal fashion, but others opt for a more tranquil existence of harmlessly hiding in their hosts. BPs and ZoeJ naturally go for the latter path, so Hatfull's team modified them by deleting the gene that keeps them peaceful. Unrestrained, these modified microbes could kill *M. abscessus* as well as Muddy.

Last June, the London team started injecting all three phages—one natural and two modified—into the patient. She didn't experience any major side effects, and after a month of twice-daily doses, the infection in her chest began to disappear. Shortly after, her liver cleared up. After six months, almost all the other lesions had faded. "It's not like she's out of the woods, in the sense that she has cystic fibrosis and a new set of lungs," Hatfull says, "but she's in very good general health."

As with any single case of medical success, it is impossible to truly know whether the supposed treatment was what eventually saved the patient: That's why doctors run clinical trials. But Benjamin Chan of Yale University says that this "fantastic" study "very nicely shows a probable impact of the phages." After all, the patient's infections clearly weren't going away on their own, and they weren't responding to other treatments.

Phages were commonly used to treat infections in the 1920s, and though they're still used in Russia and parts of eastern Europe, they largely fell out of favor in the West. But they've stepped back into the limelight after a growing line of dramatic success stories. The most famous case involves Steffanie Strathdee, an epidemiologist who led the hunt for phages that ultimately cured her husband, Tom Patterson, of a life-threatening infection. Such successes have prompted a renewed interest in phage therapy, especially in the era of antibiotic-resistant superbugs.

The London patient's case is a milestone—she is the first person to be treated with phages that have been genetically engineered. "It requires trust to take a leap off the edge into completely unknown medicine," says Hatfull, who appreciates that many people might be unnerved by his team's work. "The idea of using a virus in the first place is challenging, let alone messing around with it," he acknowledges.

He clarifies that his team simply deleted a gene that both BPs and ZoeJ would switch off naturally, when they eventually decide to flip from passive stowaways to active killers. The team also didn't *add* any genes from other organisms into the phages—an important distinction, which meant that, under UK and European Union regulations, the viruses didn't count as genetically modified organisms.

This case also represents a second milestone: It's the first time phages have successfully treated a mycobacterial infection in a human. That's huge. These microbes include the one that causes tuberculosis. They also include a group of more than 100 species called the NTMs, which often hit people with cystic fibrosis. *M. abscessus* and other opportunistic germs belong to this group."Treating NTMs is a big deal," Chan says. "It's a very unmet need in the cystic-fibrosis community."

But Muddy, ZoeJ, and BPs aren't cure-alls for these infections. *M. abscessus* is incredibly diverse, and a phage that kills one strain might do nothing against another. The London team learned that the hard way. It treated a second young girl with cystic fibrosis, who also had a double lung transplant, and who came down with a different strain of *M. abscessus*. And against that strain, Hatfull struggled to find any effective phages, despite his extensive collection. By the time he identified one, it was too late. The second patient had died.

To reliably treat any given NTM infection, scientists will need much larger phage libraries. "That's not the case for many other bacteria, like *E. coli* or *Staphylococcus aureus*, where strains are more broadly susceptible to commonly isolated phages," Chan says. But even in those cases, it's time-consuming to identify, grow, and perhaps even modify the right virus for every single case. "The challenge is whether you could ever make phage therapy broad enough so you could have an off-the-shelf set at your disposal, which you knew could infect any strain that was out there," Hatfull says. He doubts that's possible for *M. abscessus*, or indeed for most infections. That's probably why at least one trial, in which doctors tested the same cocktail of 12 phages in patients with infected burn wounds, was a bust.

"For the many infections where you have this great variability, it's going to be hard to figure out how to get phages to span it all," he says. And without that consistency, it might also be hard for phages to get significant investments from pharmaceutical companies, and

to go from the stuff of individual miracles to the stuff of generalized medicine.

http://bit.ly/2HqVby6

Kissing may be a neglected route for passing on throat gonorrhoea

Australian study reveals risks for gay and bisexual men.

Andrew Masterson reports.

Public health campaigns regarding gonorrhoea should include advice on oral hygiene, researchers suggest.

The act of kissing has been revealed as a previously neglected route for the transmission of gonorrhoea among men who have sex with other men (MSM).

A questionnaire-based study led by Eric Chow from Monash University in Melbourne, Australia, published in the journal *BMJ Sexually Transmitted Infections*, found that men who kissed multiple male partners in a three-month period had between 46% and 81% higher odds of contracting throat, or oropharyngeal, gonorrhoea compared to men who kissed only one partner, or for whom kissing did not form part of the sexual regimen.

"These data suggest that kissing may be associated with transmission of oropharyngeal gonorrhoea in MSM, irrespective of whether sex also occurs," the researchers conclude.

To make the finding, Chow and colleagues invited gay and bisexual clients to a major public sexual health service in Melbourne to fill out a survey regarding sexual encounters over the preceding three months. The questions asked whether, and how often, intimate encounters with other men involved kissing-only, kissing with sex, or sex without kissing.

The exercise ran throughout 2016 and more than 3000 men agreed to do the paperwork.

Among the cohort, just over 6% presented with throat gonorrhoea. The highest rates were among men who had four or more partners who kissed, whether or not sex occurred.

The results, write the researchers, if confirmed by further studies, indicate that public health campaigns aimed at stopping gonorrhoea transmission among the MSM community may not be adequate.

Current prophylactic advice centres on the use of condoms. Chow and colleagues suggest new approaches should "open up preventive options such as antibacterial mouthwash".

http://bit.ly/2VTMH9t

A cup of joe and you're good to go!

(Under 6 a day and you're A-OK)

Latte, cappuccino or short black, a morning coffee is an essential for many people looking to kick start their day. But while the humble coffee may be a vital feature of the daily grind, how much is too much?

While the pros and cons of drinking coffee have been debated for decades, new research from the University of South Australia reveals that drinking six or more coffees a day can be detrimental to your health, increasing your risk of heart disease by up to 22 per cent.

In Australia, one in six people are affected by cardiovascular disease. It is a major cause of death with one person dying from the disease every 12 minutes. According to the World Health Organization, cardiovascular disease is the leading cause of death, yet one of the most preventable.

Investigating the association of long-term coffee consumption and cardiovascular disease, UniSA researchers Dr Ang Zhou and Professor Elina Hyppönen of the Australian Centre for Precision Health say their research confirms the point at which excess caffeine can cause high blood pressure, a precursor to heart disease.

This is the first time an upper limit has been placed on safe coffee consumption and cardiovascular health.

"Coffee is the most commonly consumed stimulant in the world - it wakes us up, boosts our energy and helps us focus - but people are always asking 'How much caffeine is too much?'," Prof Hyppönen says.

"Most people would agree that if you drink a lot of coffee, you might feel jittery, irritable or perhaps even nauseas - that's because caffeine helps your body work faster and harder, but it is also likely to suggest that you may have reached your limit for the time being.

"We also know that risk of cardiovascular disease increases with high blood pressure, a known consequence of excess caffeine consumption.

"In order to maintain a healthy heart and a healthy blood pressure, people must limit their coffees to fewer than six cups a day - based on our data six was the tipping point where caffeine started to negatively affect cardiovascular risk."

Using UK Biobank data of 347,077 participants aged 37-73 years, the study explored the ability of the caffeine-metabolizing gene (CYP1A2) to better process caffeine, identifying increased risks of cardiovascular disease in line with coffee consumption and genetic variations.

Prof Hyppönen says that despite carriers of the fast-processing gene variation being four times quicker at metabolising caffeine, the research does not support the belief that these people could safely consume more caffeine, more frequently, without detrimental health effects.

"An estimated three billion cups of coffee are enjoyed every day around the world," Prof Hyppönen says. "Knowing the limits of what's good for you and what's not is imperative.

"As with many things, it's all about moderation; overindulge and your health will pay for it."

http://bit.ly/2W29jo4

Another Study Found a Link Between Parkinson's Disease and the Appendix. What's Going On?

Clumps of proteins found in the brains of people who have Parkinson's disease are also found somewhere else in the body — inside the appendixes of healthy people.

By Yasemin Saplakoglu, Staff Writer

This finding has led researchers to study the link between the appendix and the risk of developing Parkinson's. For example, an October 2018 study found that removing the appendix was associated with a decreased risk of developing the disorder, Live Science reported.

But new findings suggest the opposite — removing the appendix is associated with an increased risk of developing Parkinson's. The study, which has yet to be published in a peer-reviewed journal, will be presented later this month at Digestive Disease Week, a scientific meeting focused on digestive diseases.

The new study looked at data on more than 62 million patients, using a database of records from 26 major healthcare systems across the U.S. The researchers identified patients who had appendectomies — surgery to remove the appendix — and flagged those who went on to develop Parkinson's disease at least six months later.

The scientists found that, out of the more than 488,000 patients who had their appendixes removed, 4,470 (0.9%) of them went on to develop Parkinson's disease. Of the remaining 61.7 million patients who didn't have appendectomies, only around 177,000 (0.3%) later developed Parkinson's.

The findings suggest that the risk of developing Parkinson's disease is around three-fold higher for people who had appendectomies than those who did not, regardless of age, gender or race.

However, senior author Dr. Gregory Cooper, a professor of medicine at Case Western Reserve University in Cleveland, said, "at this point it's still an association," and not a cause-and-effect finding. In other words, the study does not prove that having the appendix removed causes Parkinson's.

One possible explanation for the increased risk found in the study is that, during an appendectomy a specific agent – called alpha-synuclein proteins – are released into the body and travel up to the brain, Cooper said. These proteins are known to form clumps called Lewy bodies — a tell-tale sign of Parkinson's disease.

Still, this explanation is "speculative," Cooper told Live Science.

Reverse causality?

Viviane Labrie, an assistant professor of neuroscience at Van Andel Research Institute in Michigan who was not a part of the new research, noted that the study "doesn't have a long follow-up window." That means that the researchers could only link appendectomies to the onset of Parkinson's movement problems, she said.

But these movement problems, or motor symptoms, don't truly represent the onset of the disease, Labrie told Live Science. Rather, Parkinson's disease has a roughly 20 year "prodromal period,"before these tell-tale symptoms appear. During this time, other less-obvious symptoms may occur.

For example, during the prodromal period, people with Parkinson's may experience symptoms such as constipation or other digestive issues, Labrie said. But, complicating matters further, those symptoms can increase the risk of appendicitis — the inflammatory condition that leads to an appendectomy. So, it's possible that the prodromal symptoms of Parkinson's disease may be causing the appendicitis and the subsequent surgery, and not the appendix removal causing Parkinson's disease, she said.

Labrie was the senior author of a study published in October 2018 in Science Translational Medicine, which used data from a Swedish database of more than 1.6 million people that tracked patients for up to 52 years. That report found that people who had their appendix removed when they were young were 19% to 25% less likely to develop Parkinson's later in life.

The "key difference between [the Swedish] study and the [new] US study is [the] length of time the patients were followed," Labrie said.

Cooper agreed that a limitation of his study involved the limited data available during the follow-up period. This is because the patient information was de-identified, so the researchers couldn't see how long it took for specific patients to develop Parkinson's after an appendectomy. But because the database has been gathering data since 1997, at least some of the patients were followed for nearly 30 years, he said.

In addition, the researchers didn't have access to patient medical records, so they couldn't look at other factors that may have influenced the results, such as specific symptoms or medications, Cooper added.

The risk is still really low

Ultimately, there still isn't a consensus on if appendectomies are associated with a higher risk of Parkinson's disease.

A 2016 study published in the journal Movement Disorders found similar results to this new study — that an appendectomy was associated with an increased risk of Parkinson's disease risk 10 or more years after the surgery; but that risk was much smaller than that noted in the recent study. Other research, such as a 2018 paper published in Movement Disorders, found little to no association between appendectomies and Parkinson's disease.

In any case, Cooper stressed that while the study did find an association between an appendectomy and the risk of developing Parkinson's disease, the risk is very low: Less than 1% of people

who developed Parkinson's disease had undergone an appendectomy, he said.

"I don't want people to come out of here and say, 'Well, I have appendicitis I'm not going to get my appendix taken out because I don't want to get Parkinson's disease'," he said. "If you have appendicitis … you should get your appendix out."

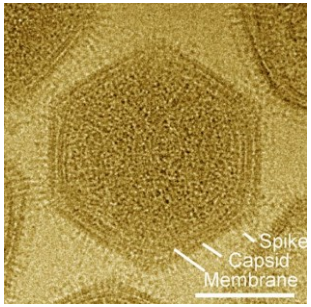
This was reminiscent of what Labrie told Live Science last fall, when her paper was published: "One of the things that we don't want to get across to people is that [they] should be having preventative appendectomies or that just because you have an appendix, you're going to get Parkinson's disease."

http://bit.ly/2VCaf3r

Medusavirus: Newly-Discovered Giant Virus Turns Its Hosts into 'Stone'

A team of researchers has isolated a new giant virus from hot spring water in Japan. Named medusavirus, the virus infects a species of amoeba called* Acanthamoeba castellanii *and can turn its host into a stone-like cyst.

May 10, 2019 by News Staff / Source



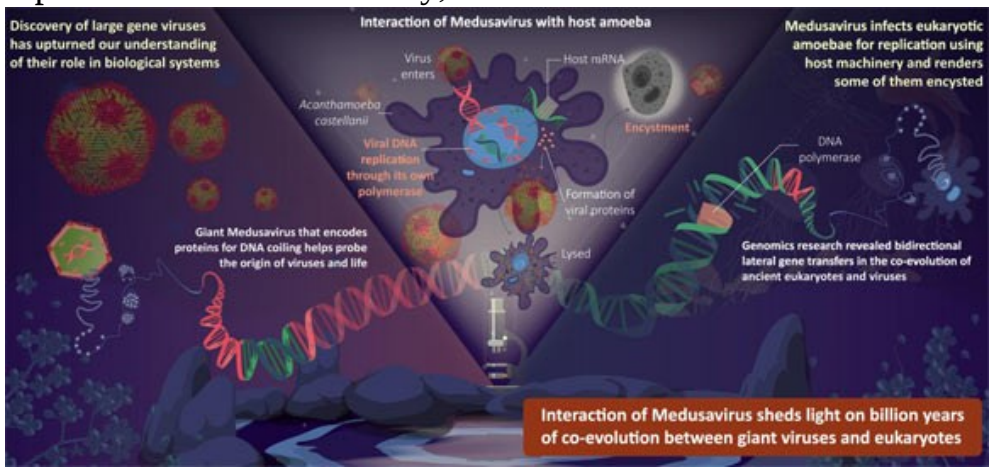
Cryo-EM image of a DNA-filled medusavirus particle viewed from a 3-fold axis; spike, capsid, and membrane are labeled. Scale bar – 100 nm.
Yoshikawa *et al*, doi: 10.1128/JVI.02130-18.

"Medusavirus is a nucleocytoplasmic large DNA virus that belongs to a group of recently discovered eukaryotic viruses with large and complex double-stranded DNA genomes."

Medusavirus, with a diameter of 260 nm, has a icosahedral capsid with unique spherical-headed spikes on its surface.

It is the first giant virus isolated from a heated environment (110 degrees Fahrenheit, or 43.4 degrees Celsius), and it shows several unique features in its replication cycle and particle morphology.

Based on the dissimilarities with other known giant viruses, Professor Takemura and co-authors proposed that medusavirus represents a new viral family, Medusaviridae.



***Medusavirus may help scientists better understand the origins of DNA replication and the evolution of complex life.* Tokyo University of Science.**

"Unlike most viruses, medusavirus contains genes that encode for proteins involved in DNA packaging," the scientists said.

"The virus has a full set of histones, which are proteins that have evolved to keep the DNA folded inside the nucleus and regulate gene expression."

"This is particularly strange, as we consider that viruses have no nucleus. This could mean that during the co-evolution, the virus might have acquired the genes that encode these histones."

When medusavirus petrifies the *Acanthamoeba castellanii* amoeba, it does so by hijacking the cell directly from its nucleus.

The virus transfers its DNA to initiate replication and uses its own DNA polymerase (enzyme that synthesizes DNA) and histones, but overall, it relies on the host to complete the process.

The results of an evolutionary analysis done by the researchers suggest that in the evolution tree, the medusavirus DNA polymerase lies at the origin of the DNA polymerase found in eukaryotes.

“This could mean that our DNA polymerase probably originated from medusavirus or one of its relatives,” said Dr. Genki Yoshikwa, a scientist at Kyoto University.

The discovery is reported in a paper in the *Journal of Virology*.

G. Yoshikawa et al. *2019. Medusavirus, a novel large DNA virus discovered from hot spring water*. J Virol *93: e02130-18; doi: 10.1128/JVI.02130-18*

https://bbc.in/2JyUa73

MPs call for 'life-changing' Kuvan to be made affordable

A number of MPs are calling on a drug company to make a "life-changing" treatment affordable to UK patients.

By Deborah Cohen BBC Newsnight

Citing a BBC Newsnight report, MPs across several parties have written to BioMarin, which markets Kuvan but did not initially discover it. The drug, which helps people who have PKU - a rare inherited disorder - is currently not available to NHS patients, as it costs £70,000. BioMarin says the NHS has not accepted its "very competitive" offer.

People with PKU (phenylketonuria) - which affects between one in 10,000 and one in 14,000 people in England - cannot properly digest the amino acid phenylalanine.

Amino acids are the building blocks of protein and are broken down by the body to make our own proteins. But in people with PKU the levels build up, and can cause brain damage.

Kuvan reduces the levels of phenylalanine in many people who have PKU.

The MPs, who include Foreign Secretary Jeremy Hunt and shadow chancellor John McDonnell, say that BioMarin did not even discover the drug itself but licensed it from a laboratory in Switzerland. It was then researched, using public money, as a treatment for PKU.

"It seems likely that development costs associated with licensing this treatment have been recouped," the MPs said in their letter, adding: "It is matter of public record that BioMarin has generated substantial revenues from Kuvan."

Louise Moorhouse, 35, knows at first-hand the difference Kuvan can make. In her early 20s she took part in trials while it was being developed by the US biotech company.

"Kuvan allowed me to eat a completely normal diet. It was almost like someone had opened curtains on my life and I could see everything in Technicolor," she told Newsnight.

"It just freed me up so much."

After the trial, Louise was denied further access to Kuvan, but since Newsnight's investigation, BioMarin has said all ex-trial patients will be treated.

However, in their letter, MPs say: "BioMarin currently has no competition for pharmacological treatments for PKU. This monopoly position carries a particular obligation to have regard to your responsibility to patients. "BioMarin needs to prioritise making this treatment available at an appropriate price across the UK as soon as possible."

The letter, signed by 17 MPs so far and originated from the office of MP Liz Twist, comes amid growing concern about the prices of drugs for rare illnesses across Europe.

Under a European incentive scheme to encourage companies to produce treatments for so-called orphan diseases, companies are

granted up to 12 years market exclusivity. This is currently under review.

The Dutch government, for example, is looking at issuing compulsory licenses if a company does not make a drug affordable. This means another company will be allowed to make the drug at a cheaper price, even when it doesn't hold the patent. We will continue to campaign for Kuvan to be made available in the UK.

***Drug companies like BioMarin need to take a more human approach and realise high prices mean many people in the UK do not have access to Kuvan, and as a result do not live the healthy lives they deserve to.* — Liz Twist MP (@LizTwistMP) April 25, 2019**

BioMarin says the "burden and severity of PKU as a disease in the UK is not recognised by NICE or the NHS".

"Under current cost-effectiveness criteria, [the] NHS expects discount in the range of 80%, making it very difficult to reach a mutually acceptable agreement," the company said in a statement.

An NHS England spokesperson said: "The NHS does not offer a blank cheque to pharmaceutical companies. Instead, the NHS works hard to strike deals which give people access to the most clinically effective and innovative medicines, and at a price which is fair and affordable, which is exactly what our patients and the country's taxpayers would expect us to do."

http://bit.ly/2Q20HIP

The looming threat of C-diff

The risk of a major gut-bug epidemic looms behind the search for a stronger antibiotic.

Neil Dowling reports.

The freshly rolled lawn you walk on, the potatoes you boil, the bacon under the eggs on a brunch plate and the handshake of a friend in hospital can transmit a bug so tenacious, so resistant to eradication and so adept at being invisible to detection that it will kill you.

It is so clever at outwitting attempts to destroy it because the anaerobic *Clostridium difficile* – dubbed *C-diff* – bacteria has existed for hundreds of millions of years. Only in the past 40 has it come onto the radar of medical researchers and only in the last 15 has it been the subject of increasingly intense research.

C-diff, now well known to hospitals around the world, is, in layman's terms, a particularly nasty tummy bug. It survives because the patient has a gut that has poor bacterial flora, allowing it to, literally, flourish.

Infection can be facilitated by issues such as poor health and ingesting spores of the bacteria which establish in a gut compromised by doses of antibiotics that have killed off the good bacteria.

But it is clouded by myths. People presume that, as with a lot of infections found in hospital patients, *C-diff* is the result of hospitalisation. It is also seen as a disease that affects only the elderly and infirm.

But more recent research finds that *C-diff* infection has no preference for age, and is now regarded as a community-borne disease not necessarily sourced from a hospital. It has been found on root vegetables in suburban grocery stores, for instance, and in roll-out lawn that was fertilised by faeces from animal farms.

In 1978, US researcher John Bartlett was the first to find what was causing an outbreak of diarrhoea-related illnesses and, in many cases, deaths. What brought the bug to international infamy was a spectacular and alarming increase in reported cases in North America in the early 2000s.

Clostridium difficile was identified as one of the most virulent causes of colitis, the inflammation of the colon wall, and subsequent diarrhoea. Cases spiked in 2002, rising from 40 to 160 patients per 100,000 in Canada. Most were elderly – in a single year, 860 people aged over 68 were hospitalised.

But the real problem hit in 2004 in Quebec when, dramatically and with unprecedented speed, 7004 cases of *C-diff* were diagnosed.

To put that in perspective, Quebec Province has a population of seven million, meaning that the bug infected one citizen in every 1000. There were not many options for treatment, and very, very few people even knew what it was. As many as 2000 died.

Australia's leading researcher on *C-diff*, Thomas Riley of Murdoch and Edith Cowan University in Perth, Western Australia, describes the Quebec outbreak as "massive". "The Canadian government spent millions and millions of dollars trying to deal with it," he says. They were unsuccessful. It began to spread, and Australia, at the other end of the globe, wasn't immune. In 2009, six cases were recorded. "But it never established itself in Australia because it was in a different environment," Riley says.

"Three hundred million years ago *C-diff* was everywhere. All the continents were joined, and the bacterium was the same across the entire land mass. Now we have different clades (or types) and we know that certain parts of the globe have certain clades of *C-diff*.

"We also have increased migration of people, and that has brought the different clades into new parts of the world. The clade from Africa, for example, has been recently identified in Europe and Australia because of migration.

"Asian strains have likely been in California since the gold rush of the late 1800s brought Chinese migrants. At one stage, the Chinese represented 10% of the Californian population."

So the bug proliferated. In 2013, it was responsible for 29,000 deaths in the US alone. The annual reported cases in the US total 400,000. Now the job is to find the antibiotic that will kill *C-diff* but not kill the beneficial bacteria in the human gut.

The search is heavily funded by private and public donations in the US. Globally, it is the subject of four international conferences each year.

"*C-diff* cannot survive in a normal human gut," Riley says.

"We now know it's also a community-acquired infection and that patients are getting younger. There is very little cross-infection in Australia, and only 25% of cases have links to the patient visiting a hospital.

"We do know that it is coming from animals. In Australia, 60% of dairy calves tested had *C-diff*. In intensive pig farming, piglets at the age of seven days are full of it. Yet at age 21 days, they have none."

Su-Chen Lim, who did her PhD with Riley on the presence of *C-diff* in root vegetables, says 50% of potatoes in Australian supermarkets were contaminated. Onions imported from California were likely a major source of the bacteria during a shortage some years ago.

"The rate in compost and mulch sold at gardening shops is 30% containing C-diff while in roll-out lawn the rate is double, at 60% of samples being found with the bacteria," she says. "It comes from animal manure."

The problem with food is that scrubbing root vegetables will just contaminate the kitchen environment with the bacteria.

"And conventional cooking temperatures won't kill the *C-diff* spores because they are resistant," she warns. "Curing of meat also doesn't kill the bacteria."

But there is an answer. In fact, two. One is a drug called Fidaxomicin – very expensive and definitely not government subsidized. The other, the one in which researchers including Riley hold great hope, is a new drug Ridinilazole.

Ridinilazole is now in Phase-3 clinical trials and is expected to become available in about two years.

Ironically, without this type of antibiotic to kill a bug that thrives because its competition has been killed by other antibiotics, Riley warns: "We have the potential for a nasty outbreak."