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In one cancer therapy, two halves are safer than a whole

Splitting immunotoxins in half could increase their specificity toward cancers, study suggests

COLUMBUS, Ohio - Splitting one type of cancer drug in half and delivering the pieces separately to cancer cells could reduce life-threatening side effects and protect healthy, non-cancerous cells, a new study suggests. The study, published today in the *Proceedings of the National Academy of Sciences*, suggests that splitting immunotoxins into two inactive and benign parts may set the stage for future, targeted treatments of cancers.

Immunotoxins combine an immune substance with a toxin. The immune substance attaches to cancer cells, allowing the toxin to enter the cancer cell and kill it without harming nearby healthy cells. The research was designed as a proof-of-concept study, but the researchers found that the functional toxin can be reconstructed in cancer cells in both laboratory cell cultures and in mice.

The search for a cancer cure has led to a number of treatments that destroy cancer cells, but also destroy healthy, non-cancerous cells. That destruction often causes life-threatening side effects.

"The problem is not to kill the healthy cells," said Dmitri Kudryashov, an associate chemistry professor at The Ohio State University and senior author of the study. "What is difficult is to kill only the cancer cells and nothing else." And while some cancer treatments have been successful at targeting cancer cells, few have been able to do so without also affecting healthy cells.

The key to split immunotoxins is that only cancer cells will receive both parts of the split toxin, said Elena Kudryashova, a co-senior author on the study and a research scientist at Ohio State. "We have confirmed that when separated, the parts of the split toxin do not harm cells. But when they recombine into the original toxin, the treatment destroys the cancer.

"But to achieve that, both parts must enter cancer cells," Kudryashova said. "What we have achieved so far is the reconstruction of the fully functional toxin upon specific delivery of one part of the split immunotoxin to the cells expressing the other part. The specific delivery of this other part in sufficient quantity is yet to be achieved and is being pursued in the laboratory."

Essentially, when the toxin protein is split and goes into the human body as a cancer treatment, it can't cause harm to healthy cells. But if biochemists can find a way to get both pieces of the protein to enter a cancer cell, the two pieces of toxin can then destroy the cancer.

Other Ohio State researchers who worked on this study are a lead author, Vedud Purde, and David Heisler and Reena Shakya.

This work was funded by the National Cancer Institute and a Pelotonia Idea Grant.

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Are antivitamins the new antibiotics?

Research team from University of Göttingen develops drug approach against bacterial infections

Antibiotics are among the most important discoveries of modern medicine and have saved millions of lives since the discovery of penicillin almost 100 years ago. Many diseases caused by bacterial infections - such as pneumonia, meningitis or septicaemia - are successfully treated with antibiotics. However, bacteria can develop resistance to antibiotics which then leaves doctors struggling to find effective treatments. Particularly problematic are pathogens which develop multi-drug resistance and are unaffected by most antibiotics. This leads to severe disease progression in affected patients, often with a fatal outcome. Scientists all over the world are therefore engaged in the search for new antibiotics. Researchers at the University of Göttingen and the Max Planck Institute for

Biophysical Chemistry Göttingen have now described a promising new approach involving "antivitamins" to develop new classes of antibiotics. The results were published in the journal *Nature Chemical Biology*.

Antivitamins are substances that inhibit the biological function of a genuine vitamin. Some antivitamins have a similar chemical structure to those of the actual vitamin whose action they block or restrict. For this study, Professor Kai Tittmann's team from the Göttingen Center for Molecular Biosciences at the University of Göttingen worked together with Professor Bert de Groot's group from the Max Planck Institute for Biophysical Chemistry Göttingen and Professor Tadgh Begley from Texas A&M University (USA). Together they investigated the mechanism of action at the atomic level of a naturally occurring antivitamin of vitamin B1. Some bacteria are able to produce a toxic form of this vital vitamin B1 to kill competing bacteria. This particular antivitamin has only a single atom in addition to the natural vitamin in a seemingly unimportant place and the exciting research question was why the action of the vitamin was still prevented or "poisoned".

Tittmann's team used high-resolution protein crystallography to investigate how the antivitamin inhibits an important protein from the central metabolism of bacteria. The researchers found that the "dance of the protons", which can normally be observed in functioning proteins, almost completely ceases to function and the protein no longer works. "Just one extra atom in the antivitamin acts like a grain of sand in a complex gear system by blocking its finely tuned mechanics," explains Tittmann. It is interesting to note that human proteins are able to cope relatively well with the antivitamin and continue working. The chemist de Groot and his team used computer simulations to find out why this is so. "The human proteins either do not bind to the antivitamin at all or in such a way that they are not 'poisoned'," says the Max Planck researcher. The difference between the effects of the antivitamin on bacteria and on human proteins opens up the possibility of using it as an antibiotic in the future and thus creating new therapeutic alternatives.

The research project was funded by the German Research Foundation (DFG).
Original Publication: F. Rabe von Pappenheim et al. Structural basis for antibiotic action of the B1 antivitamin 2?-methoxy-thiamine. Nature Chemical Biology (2020).
https://doi.org/10.1038/s41589-020-0628-4
Or: https://www.nature.com/articles/s41589-020-0628-4

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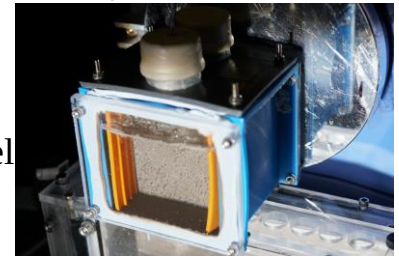
Wireless device makes clean fuel from sunlight, CO2 and water

Standalone device that converts sunlight, carbon dioxide and water into a carbon-neutral fuel, without any additional components or electricity



Researchers have developed a standalone device that converts sunlight, carbon dioxide and water into a carbon-neutral fuel without requiring any additional components or electricity.

This device, developed by a team from the University of Cambridge, is a significant step toward achieving artificial photosynthesis - a process mimicking the ability of plants to convert sunlight into energy. It is based on an advanced 'photosheet' technology and converts sunlight, carbon dioxide and water into oxygen and formic acid - a storable fuel that can be either be used directly or be converted into hydrogen. **University of Cambridge**

The device, developed by a team from the University of Cambridge, is a significant step toward achieving artificial photosynthesis - a process mimicking the ability of plants to convert sunlight into energy. It is based on an advanced 'photosheet' technology and converts sunlight, carbon dioxide and water into oxygen and formic acid - a storable fuel that can be either be used directly or be converted into hydrogen.

The results, reported in the journal *Nature Energy*, represent a new method for the conversion of carbon dioxide into clean fuels. The wireless device could be scaled up and used on energy 'farms' similar to solar farms, producing clean fuel using sunlight and water.

Harvesting solar energy to convert carbon dioxide into fuel is a promising way to reduce carbon emissions and transition away from fossil fuels. However, it is challenging to produce these clean fuels without unwanted by-products.

"It's been difficult to achieve artificial photosynthesis with a high degree of selectivity, so that you're converting as much of the sunlight as possible into the fuel you want, rather than be left with a lot of waste," said first author Dr Qian Wang from Cambridge's Department of Chemistry.

"In addition, storage of gaseous fuels and separation of by-products can be complicated - we want to get to the point where we can cleanly produce a liquid fuel that can also be easily stored and transported," said Professor Erwin Reisner, the paper's senior author.

In 2019, researchers from Reisner's group developed a solar reactor based on an 'artificial leaf' design, which also uses sunlight, carbon dioxide and water to produce a fuel, known as syngas. The new technology looks and behaves quite similarly to the artificial leaf but works in a different way and produces formic acid.

While the artificial leaf used components from solar cells, the new device doesn't require these components and relies solely on photocatalysts embedded on a sheet to produce a so-called photocatalyst sheet. The sheets are made up of semiconductor powders, which can be prepared in large quantities easily and cost-effectively.

In addition, this new technology is more robust and produces clean fuel that is easier to store and shows potential for producing fuel products at scale. The test unit is 20 square centimetres in size, but the researchers say that it should be relatively straightforward to scale it up to several square metres. In addition, the formic acid can be accumulated in solution, and be chemically converted into different types of fuel. "We were surprised how well it worked in terms of its selectivity - it produced almost no by-products," said Wang. "Sometimes things don't work as well as you expected, but this was a rare case where it actually worked better."

The carbon-dioxide converting cobalt-based catalyst is easy to make and relatively stable. While this technology will be easier to scale up than the artificial leaf, the efficiencies still need to be improved before any commercial deployment can be considered. The researchers are experimenting with a range of different catalysts to improve both stability and efficiency.

The current results were obtained in collaboration with the team of Professor Kazunari Domen from the University of Tokyo, a co-author of the study. The researchers are now working to further optimise the system and improve efficiency. Additionally, they are exploring other catalysts for using on the device to get different solar fuels. "We hope this technology will pave the way toward sustainable and practical solar fuel production," said Reisner.

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IKBFU scientists suggest using heather as an antioxidant

According to the scientists, this plant is a source of valuable biologically active substances with cardioprotective, neuroprotective, anti-inflammatory, antitumor, and antiviral effects

According to the scientists, this plant is a source of valuable biologically active substances with cardioprotective, neuroprotective, anti-inflammatory, antitumor, and antiviral effects.

Researchers have proven heather to be effective herbal medicinal raw material. This small relict, evergreen shrub is a widespread plant in Europe and has long been used as a medicine for the treatment of rheumatism, arthritis, as well as an antiseptic, choleretic, wound healing, expectorant. A wide range of medicinal properties of heather is determined by the diversity and high content of biologically active substances in the plant, primarily phenolic compounds, which perform many different functions, for example, they are involved in photosynthesis and plant breathing process.

Heather is not included in the list of medicinal products. However, according to the scientists, this plant is a source of valuable biologically active substances with cardioprotective, neuroprotective, anti-inflammatory, antitumor, and antiviral effects. To prove this, the staff and students of the Institute of Living Systems have been collecting common heather from May to October 2019 at four stages (beginning of vegetation, budding, flowering, and fruiting) in the Pig Swamp on the Curonian Spit. Scientists have determined the content of biologically active compounds in the leaves, stems, roots, rhizomes, flowers, and seeds, as well as the antioxidant and antibacterial activity of the extracts against the bacteria of *E. coli* and hay bacillus.

Lyubov Skrypnik, Ph.D. in Biology, Associate Professor at the Institute of Living Systems told us:

"The phytochemical composition of heather is well studied. However, there was no research on the seasonal dynamics of the quantitative content of flavonoids, tannins, anthocyanins, proanthocyanins, hydroxycinnamic acids. In addition, earlier most of the studies were devoted to the study of the aboveground part of the heather, but in our work, we proved that phenolic compounds are actively accumulating in underground organs - the roots and rhizomes of the plant. Typically, heather is harvested for medicinal purposes during the flowering stage. But in the course of the study, we found that the maximum amount of flavonoids, which are of the greatest medicinal value, accumulates in all organs of the heather during the budding phase. This leads to a recommendation for harvesting heather plants just before flowering. Additionally, it was found that the budding stage is the only stage at which the antibacterial activity of the extracts of all the studied parts of the plant was found simultaneously, and the leaves and stems showed an antibacterial effect against bacteria of *E. coli* and hay bacillus".

The results of the research were published in the "Plants" scientific journal. The research was conducted by IKBFU Institute of Living Systems students Viktoriya Chepel and Valeriy Lisun, under prof. Lyubov Skrypnik.

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How dinosaur research can help medicine

Even Tyrannosaurus rex could have suffered a slipped disc

The intervertebral discs connect the vertebrae and give the spine its mobility. The disc consists of a cartilaginous fibrous ring and a gelatinous core as a buffer. It has always been assumed that only humans and other mammals have discs. A misconception, as a research team under the leadership of the University of Bonn has now discovered: Even Tyrannosaurus rex could have suffered a slipped disc. The results have now been published in the journal *"Scientific Reports"*.

Present-day snakes and other reptiles do not have intervertebral discs; instead, their vertebrae are connected with so-called ball-and-socket joints. Here, the ball-shaped end surface of a vertebra fits into a cup-shaped depression of the adjacent vertebra, similar to a human hip joint. In-between there is cartilage and synovial fluid to keep the joint mobile. This evolutionary construction is good for today's reptiles, because it prevents the dreaded slipped disc, which is caused by parts of the disc slipping out into the spinal canal.

"I found it hard to believe that ancient reptiles did not have intervertebral discs," says paleontologist Dr. Tanja Wintrich from the Section Paleontology in the Institute of Geosciences of the University of Bonn. She noticed that the vertebrae of most dinosaurs and ancient marine reptiles look very similar to those of humans - that is, they do not have ball-and-socket joints. She therefore wondered whether extinct reptiles had intervertebral discs, but had "replaced" these with ball-and-socket joints in the course of evolution.

Comparison of the vertebrae of dinosaurs with animals still alive today

To this end, the team of researchers led by Tanja Wintrich and with the participation of the University of Cologne and the TU Bergakademie Freiberg as well as researchers from Canada and Russia examined a total of 19 different dinosaurs, other extinct reptiles, and animals still alive today. The researchers concluded that intervertebral discs not only occur in mammals. For these investigations, vertebrae still in connection were analyzed using various methods.

Surprisingly, Dr. Wintrich has now also been able to demonstrate that remnants of cartilage and even other parts of the intervertebral disc are almost always preserved in such ancient specimens, including marine reptiles like ichthyosaurs and dinosaurs like Tyrannosaurus. She then traced the evolution of the soft tissues between the vertebrae along the family tree of land animals, which 310 million years ago split into the mammalian line and the dinosaur and bird line.

Intervertebral discs emerged several times during evolution

It was previously unknown that intervertebral discs are a very ancient feature. The findings also show that intervertebral discs evolved several times during evolution in different animals, and were probably replaced by ball-and-socket joints twice in reptiles. "The reason why the intervertebral disc was replaced might be that it is more susceptible to damage than a ball-and-socket joint," says Dr. Wintrich. Nonetheless, mammals have always retained intervertebral discs, repeating the familiar pattern that they are rather limited in their evolutionary flexibility. "This insight is also central to the medical understanding of humans. The human body is not perfect, and its diseases reflect our long evolutionary history," adds paleontologist Prof. Dr. Martin Sander from the University of Bonn.

In terms of research methods, the team drew not only on paleontology, but also on medical anatomy, developmental biology and zoology. Under the microscope, dinosaur bones cut with a rock saw and then ground very thinly provide information comparable to histological sections of fixed and embedded tissue of extant animals. This makes it possible to bridge the long periods of evolution and identify developmental processes. Prof. Sander remarks: "It's truly amazing that the cartilage of the joint and apparently even the disc itself can survive for hundreds of millions of years."

Dr. Wintrich, who now works at the Institute of Anatomy of the University of Bonn, is pleased about the cooperation between the fields that has made this interdisciplinary understanding possible in the first place: "We found that even Tyrannosaurus rex was not protected against slipped discs." Only bird-like predatory dinosaurs then evolved ball-and-socket joints as well and saddle joints, still seen in today's birds. Likewise, such ball-and-socket joints were a decisive advantage for the stability of the spine of the largest dinosaurs, the long-necked dinosaurs.

This bridge between paleontology and medicine is seminal in Germany. The anatomist Prof. Dr. Karl Schilling from the University of Bonn, who was not involved in the new study, reports: "In the USA, in contrast, dinosaur researchers and evolutionary biologists are often closely involved in medical

training, especially in anatomy and embryology. This gives young doctors a perspective that is becoming increasingly important in a rapidly changing environment."

Publication: *Tanja Wintrich, Martin Scaal, Christine Böhmer, Rico Schellhorn, Ilja Kogan, Aaron van der Reest & P. Martin Sander: Paleontological evidence reveals convergent evolution of intervertebral joint types in amniotes, Scientific Reports, DOI:10.1038/s41598-020-70751-2*

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Deep chest compressions prevent brain damage during cardiac arrest

Deep chest compressions can crack ribs, but they reduce brain damage during cardiac arrest

Sophia Antipolis, France - Deep chest compressions can crack ribs, but they reduce brain damage during cardiac arrest, reports a study presented today at ESC Congress 2020.[1]

Study author Dr. Irene Marco Clement of University Hospital La Paz, Madrid, Spain said: "Deep chest compressions improve blood flow to the brain, improving survival and brain function."

CPR guidelines are updated every five years and are used to train health professionals and members of the public. The 2010 recommendation for deeper chest compressions generated concerns over the possibility of increasing CPR-related injuries.

This study examined the impact of this advice on neurological outcomes in survivors of cardiac arrest. It also assessed the rate of CPR-related injuries and their association with prognosis.

The study limited participation to comatose survivors of cardiac arrest, since they would have received prolonged resuscitation. In contrast, survivors who regain consciousness have generally received an immediate electric shock and brief chest compressions to restore circulation. "We wanted to analyse the effect of deep chest compressions during prolonged resuscitation, when they could make a real difference to outcomes," said Dr. Marco Clement.

In 2006 to 2020, the study enrolled consecutive patients admitted to an acute cardiac care unit after a cardiac arrest in hospital or in the community. Patients were divided into three groups corresponding to updates of the CPR guidelines: 2006-2010, 2011-2015, and 2016-2020.

The study included 510 patients who survived cardiac arrest and were admitted to hospital while unconscious. The average age was 63 years and 81% were men. CPR by lay bystanders and the use of automated external defibrillators (AEDs) progressively increased over the study period.

After 2010, there was a higher proportion of CPR-related injuries: 12.7% in 2006-2010, 23.5% in 2011-2015, 22.7% in 2016-2020 ($p=0.02$). Just over half of patients survived and were discharged from the hospital (51.6%). Brain performance at three months significantly increased over the course of the study (i.e. it was highest in the 2016-2020 group).[2]

Patients with CPR-related injuries were more likely to have better brain performance. Nearly two-thirds (65.1%) of patients with injuries had high brain function compared to 43.2% without injuries ($p<0.01$). The most common injuries were rib or sternal fractures.

"Survival and neurological outcome improved significantly during the 14-year study," said Dr. Marco Clement. "Members of the public increasingly came to the rescue with CPR and there was greater use of AEDs. Injuries from CPR rose, but these patients were less likely to have brain damage."

She noted that lay people have been reluctant to do CPR during the COVID-19 pandemic due to fear of infection. She said: "Personal safety always comes first, and resuscitators should only do what they feel comfortable with. If you are concerned about possible contagion, you could omit mouth-to-mouth breaths: chest compressions alone may be as effective as conventional CPR."

How to improve survival and prevent brain damage from cardiac arrest

**** Ask a bystander to call emergency services and find an AED.***

**** Start deep chest compressions immediately.***

**** Do not delay CPR by trying to find a pulse.***

Funding: None. *Disclosures: None.*

References and notes

[1]Abstract title: Impact of resuscitation guidelines updates on global outcomes after cardiac arrest.

[2]Neurological outcome after cardiac arrest was assessed using the Cerebral Performance Category (CPC) score.

https://bit.ly/31yjOBD

Can Vaccines for Wildlife Prevent Human Pandemics?

Studies suggest that self-disseminating vaccines could prevent the 'spillover' of animal viruses into humans as pandemic diseases.

Rodrigo Pérez Ortega *Writing Intern*

Scientists still debate whether the SARS-CoV-2 virus originated in a bat or a pangolin. But they are sure that this coronavirus is only the most recent example of a zoonosis — an infectious disease that passes from animals to humans. From HIV to Ebola virus, Nipah virus and bird flu, pathogens lurking in wildlife have repeatedly found a way to "spill over" into humans, as epidemiologists put it. Between 2009 and 2019, the U.S. Agency for International Development's early-warning pandemic system, PREDICT, detected more than 1,000 new viruses with zoonotic potential in wild animals. The COVID-19 pandemic will not be the last one.

But what if we could prevent the next pandemic by stopping its spread in animals before it jumped to us? Could this be achieved with vaccines that spread through a wild population on their own? Some scientists think so.

Recently in *Nature Ecology & Evolution*, a pair of biologists at the University of Idaho argued for that approach. The idea of "self-disseminating" vaccines has floated through epidemiological circles for decades, conceived mainly as a tool for protecting the health of wildlife. But the mathematical biologist Scott Nuismer and the evolutionary biologist James Bull have refreshed the proposal with evidence from their own modeling and other experimental work, which suggests that self-disseminating vaccines could be a safe and practical way to head off zoonotic pandemics as well. The idea still has hurdles to clear before it can be put into practice, but researchers reached for comment were generally intrigued by its potential.

Transferable Vaccines

Vaccinating animals for their own health and for the protection of humans is commonly done on farms. But "it's just super hard to vaccinate a wild population," Nuismer said. Bats, foxes, raccoons, boars and other wildlife that harbor potential zoonotic infections tend to hide in remote places, so vaccinating enough of them to create herd immunity is not an easy feat.

Scientists have successfully used baited vaccines to manage rabies in foxes in Western Europe and raccoons in the United States. But those vaccines protect only the individual animals that eat them, and some animals that harbor pathogens, such as bats, don't go for baits.

To get past these limitations, scientists have proposed creating self-disseminating vaccines that would naturally spread in wild populations. Nuismer and Bull discussed two kinds: transferable vaccines and transmissible ones.

A transferable vaccine can be given to a bat, for example, as a paste on its fur. Upon the animal's return to its colony, other bats would groom it and get exposed to the vaccine too. The spread of this type of vaccine would be limited, but in Nuismer and Bull's models, transferable vaccines could achieve high enough levels of immunization to potentially eradicate pathogens in wild populations.

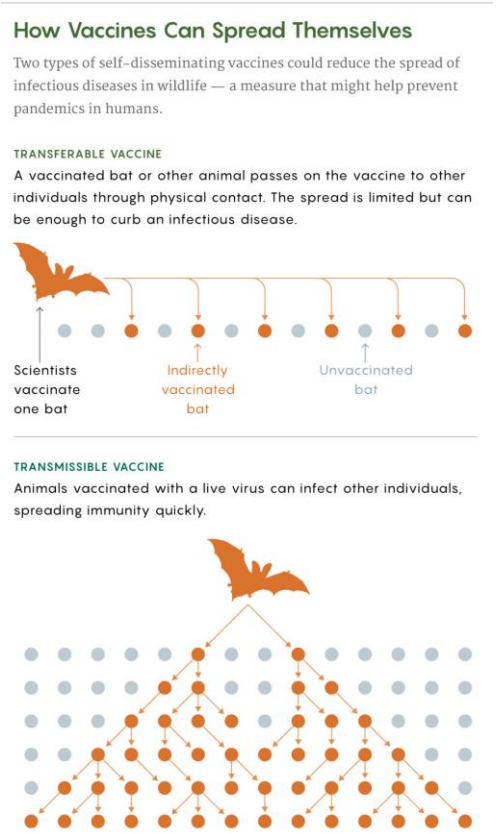
Daniel Streicker, a disease ecologist at the University of Glasgow, validated this strategy in 2017 when he traveled to Peru with his

team to test transferable vaccines in vampire bats to combat rabies, which is a significant cause of human death in South America. Even where few people get rabies, on farms "losing one or two cattle can really be devastating for families," Streicker said.

He and his team located three bat colonies, each with 200 or more bats, and smeared the backs of 20 to 60 animals in each colony with a gel containing a biomarker that made their hair fluoresce if they ingested it. Days later, the scientists found that in two of the colonies, at least 84% of the bats glowed, which suggests that a transferable vaccine applied this way could immunize enough bats to reduce the frequency, size and duration of rabies outbreaks.

With enough funding, Nuismer thinks transferable vaccines could be used relatively soon. "We can definitely do that," he said.

Pandemic prevention aside, the use of this kind of vaccine could also provide more humane control of rabies, because culling bats is currently the go-to method of keeping the disease at bay in South America.



Samuel Velasco/Quanta Magazine

Transmissible Vaccines

The second type of self-disseminating vaccine, the transmissible one, consists of live modified viruses that propagate a weakened form of a disease. They would be ideal for large wild populations because even just a few individual animals vaccinated with them could spread immunity widely.

However, as Nuismer, Bull and other researchers acknowledge, a poorly designed live virus could evolve after it was released and potentially become a pathogen again — the opposite of what researchers want. For that reason, recombinant vaccines, in which researchers insert a gene from a pathogen into an innocuous virus, might be most promising: If the inserted gene is lost through natural selection, then only the harmless vector is left. "The modeling suggests the approach could work extremely well," Nuismer said.

At least one real-world field study supports the idea that transmissible vaccines can be both safe and effective at eradicating a deadly disease in wildlife. In the 1990s, a team led by José Manuel Sánchez-Vizcaíno, a veterinarian then at the Animal Health Research Center in Madrid, created a recombinant live vaccine to protect rabbits from a lethal hemorrhagic disease. When they tested it on a small island off the coast of Spain, the vaccine seemed to spread to more than half of the local rabbit population.

Despite that apparent success, other field studies have not followed: According to Sánchez-Vizcaíno, transmissible vaccines have not drawn much interest from pharmaceutical companies because they look unprofitable. Nevertheless, he is working on a recombinant viral vaccine against African swine fever that would spread for only a few hours or days. With new molecular biology techniques, researchers can fine-tune vaccines to have predetermined lifetimes, which could eliminate concerns over unwanted mutations or ongoing evolution of the vaccine organism.

'We Have to Stop Being Reactive'

Michael Jarvis, a virologist at the University of Plymouth, leads a group that has created vaccines against Ebola and tuberculosis with cytomegaloviruses, which he says offer a great deal of flexibility as vectors. Most cytomegaloviruses don't cause disease, and each

strain has evolved to infect only one species, so the risk of a cytomegalovirus vaccine jumping between species is very low. Transmissible vaccines, he said, “potentially solve a problem that we don’t have a solution for at present.”

However, safety and ecological concerns take priority. “Whenever you’re dealing with a biological organism that you’re potentially thinking of releasing, then you need to err very heavily on the side of caution,” Jarvis said.

In addition to working on safety, researchers will need to learn more about ways to spread vaccines in various species — particularly in animals that are less gregarious than bats. To identify good targets for this intervention, epidemiologists may need more or better information about which animal diseases are on the rise, and which ones have the greatest potential for spillover to humans. Funding for the PREDICT program ran out in 2019, however, and the Trump administration officially ended it in March, although a six-month extension was granted to help study animal sources of the SARS-CoV-2 virus.

For Maria Elena Bottazzi, a vaccinologist at Texas Children’s Hospital and Baylor College of Medicine who is currently racing to produce a COVID-19 vaccine, the concept of self-disseminating vaccines to prevent spillovers “is definitely intriguing.” The effort could also help to highlight the interconnection between the health of humans, animals, plants and the environment as a whole. “We have to stop being reactive and [trying] to stop something in the middle of the crisis,” she said.

“If you look at the economics of it, it’s a no-brainer,” Streicker said. Governments and philanthropists around the world have invested billions in finding cures and vaccines for COVID-19. “Just imagine if we invested some tiny fraction of that intervention, and particularly into new strategies for prevention,” he said. “We could really make huge strides.”

https://wb.md/3jhvZJ5

First Evidence of SARS-CoV-2 in Heart Cells

It's believed to be the first evidence of direct infection of heart muscle cells by the virus; viral particles were identified in different cell lineages of the heart

Megan Brooks

SARS-CoV-2 has been found in cardiac tissue of a child from Brazil with multisystem inflammatory syndrome (MIS-C) related to COVID-19 who presented with myocarditis and died of heart failure.

It's believed to be the first evidence of direct infection of heart muscle cells by the virus; viral particles were identified in different cell lineages of the heart, including cardiomyocytes, endothelial cells, mesenchymal cells, and inflammatory cells.

The case is described in a report published online August 20 in *The Lancet Child & Adolescent Health*.

"The presence of the virus in various cell types of cardiac tissue, as evidenced by electron microscopy, shows that myocarditis in this case is likely a direct inflammatory response to the virus infection in the heart," first author Marisa Dolhnikoff, MD, Department of Pathology, University of Sao Paulo, Brazil, told *Medscape Medical News*.

There have been previous reports in adults with COVID-19 of both SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR) and viral particles by electron microscopy in cardiac tissue from endomyocardial specimens, the researchers note.

One of these reports, published in April by Tavazzi and colleagues, they write, "detected viral particles in cardiac macrophages in an adult patient with acute cardiac injury associated with COVID-19; no viral particles were seen in cardiomyocytes or endothelial cells.

"Our case report is the first to our knowledge to document the presence of viral particles in the cardiac tissue of a child affected by

MIS-C," they add. "Moreover, viral particles were identified in different cell lineages of the heart, including cardiomyocytes, endothelial cells, mesenchymal cells, and inflammatory cells."

"Concerning" Case Report

"This is a concerning report as it shows for the first time that the virus can actually invade the heart muscle cells themselves," C. Michael Gibson, MD, CEO of the Baim Institute for Clinical Research in Boston, Massachusetts, told *Medscape Medical News*.

"Previous reports of COVID-19 and the heart found that the virus was in the area outside the heart muscle cells. We do not know yet the relative contribution of the inflammatory cells invading the heart, the release of blood-borne inflammatory mediators, and the virus inside the heart muscle cells themselves to heart damage," Gibson said.

The patient was a previously healthy 11-year-old girl of African descent with MIS-C related to COVID-19. She developed cardiac failure and died after one day in the hospital, despite aggressive treatment.

SARS-CoV-2 RNA was detected on a postmortem nasopharyngeal swab and in cardiac and pulmonary tissues by RT-PCR.

Postmortem ultrasound examination of the heart showed a "hyperechogenic and diffusely thickened endocardium (mean thickness 10 mm), a thickened myocardium (18 mm thick in the left ventricle), and a small pericardial effusion," Dolhnikoff and colleagues report.

Histopathological exam revealed myocarditis, pericarditis, and endocarditis characterized by infiltration of inflammatory cells. Inflammation was mainly interstitial and perivascular, associated with foci of cardiomyocyte necrosis and was mainly composed of CD68+ macrophages, a few CD45+ lymphocytes, and a few neutrophils and eosinophils.

Electron microscopy of cardiac tissue revealed spherical viral particles in shape and size consistent with the *Coronaviridae* family in the extracellular compartment and within cardiomyocytes, capillary endothelial cells, endocardium endothelial cells, macrophages, neutrophils, and fibroblasts.

Microthrombi in the pulmonary arterioles and renal glomerular capillaries were also seen at autopsy. SARS-CoV-2-associated pneumonia was mild.

Lymphoid depletion and signs of hemophagocytosis were observed in the spleen and lymph nodes. Acute tubular necrosis in the kidneys and hepatic centrilobular necrosis, secondary to shock, were also seen. Brain tissue showed microglial reactivity.

"Fortunately, MIS-C is a rare event and, although it can be severe and life threatening, most children recover," Dolhnikoff commented. "This case report comes at a time when the scientific community around the world calls attention to MIS-C and the need for it to be quickly recognized and treated by the pediatric community. Evidence of a direct relation between the virus and myocarditis confirms that MIS-C is one of the possible forms of presentation of COVID-19 and that the heart may be the target organ. It also alerts clinicians to possible cardiac sequelae in these children," she added.

Experts Weigh In

Scott Aydin, MD, medical director, Pediatric Cardiac Intensive Care, Mount Sinai Kravis Children's Hospital in New York City, told *Medscape Medical News* this case report is "unfortunately not all that surprising."

"Since the initial presentations of MIS-C several months ago, we have suspected mechanisms of direct and indirect injury to the myocardium. This important work is just the next step in further understanding the mechanisms of how COVID-19 creates havoc in the human body and the choices of possible therapies we have to

treat children with COVID-19 and MIS-C," said Aydin, who was not involved with the case report.

Anish Koka, MD, a cardiologist in private practice in Philadelphia, Pennsylvania, noted that, in these cases, endomyocardial biopsy is "rarely done because it is fairly invasive, but even when it has been done, the pathologic findings are of widespread inflammation rather than virus-induced cell necrosis."

"While reports like this are sure to spawn viral tweets, it's vital to understand that it's not unusual to find widespread organ dissemination of virus in very sick patients. This does not mean that the virus is causing dysfunction of the organ it happens to be found in," Koka told *Medscape Medical News*.

He noted that in the case of the young girl who died, it took high PCR-cycle threshold values to isolate virus from the lung and heart samples.

"This means there was a low viral load in both organs, supporting the theory of SARS-CoV-2 as a potential trigger of a widespread inflammatory response that results in organ damage, rather than the virus itself infecting and destroying organs," said Koka, who was also not associated with the case report.

This research had no specific funding. The authors have declared no competing interests. Aydin has disclosed no relevant financial relationships. Koka has disclosed financial relationships with Boehringer Ingelheim and Jardiance.

Lancet Child Adolesc Health. Published online August 20, 2020. Case report

https://bit.ly/2YDRpIA

New blood, new hope: Transfusions protect the brain from stroke damage

Blood substitution therapy rescues the brains of mice from ischemic damage.

Muscle weakness permeates through one side of your body and your speech slurs. It's a stroke. And you need to be rushed to the emergency room. Doctors replace your blood with the blood of a healthy person who's never suffered a stroke.

This blood swap lessens damage to your brain, and any neurological deficits from the stroke are nil. This is not mere wishful thinking. It is a potential breakthrough in stroke therapy based on mice research by West Virginia University neuroscientists.

In the study, led by Xuefang "Sophie" Ren, research assistant professor in the Department of Neuroscience, the team found that blood substitution therapy rescues the brains of mice from ischemic damage. Their article is published in *Nature Communications*.

"What we were able to demonstrate is that if you remove part of the blood from a subject undergoing stroke, and replace that blood from a subject that's never had a stroke, the outcomes of that stroke are profoundly improved," said Ren, who's also director of the WVU Experimental Stroke Core.

The study is believed to be the first to show that blood replacement therapy leads to improved stroke outcomes in mice, a potential next step for stroke therapy in humans. Most strokes (ischemic) occur when the blood supply to the brain is interrupted, usually by a blockage of the arteries leading to the brain.

While there is no known single medication for stroke, the only FDA-approved treatment for ischemic strokes is tPA, or tissue plasminogen activator, which dissolves the clot and improves blood flow. However, tPA typically must be administered within three hours of the stroke.

Ren's research indicates that blood transfusions can take place beyond that limited window - up to seven hours - and still have a positive impact. Replacing 20 percent of the blood in a mouse was enough to show a profound reduction in damage to the brain. The average adult holds around one-and-a-half gallons of blood in the body. The study's co-authors include Heng Hu, postdoctoral fellow and Experimental Stroke Core surgeon, and James Simpkins, director of the Center for Basic & Translational Stroke Research and professor of the Department of Neuroscience.

Out with the old, in with the new

"The idea is to change the immune response that happens after stroke," Simpkins said.

Researchers explained that following a stroke, the makeup of a patient's blood changes, causing disruptions in the brain and how the body responds. Neutrophils, a type of white blood cell that helps lead the immune system's response, play a role in increasing the levels of an enzyme called MMP-9, which can lead to blood-brain barrier leakage and degeneration in brain tissue.

Blood replacement therapy removes inflammatory cells and decreases neutrophils and MMP-9 levels following a stroke, the study concluded.

"The immune system doesn't recognize much of what's happening when there's a stroke," Simpkins said. "So the neutrophils go to the brain and try to clean up the damage that happens. But there's too much in the brain and those same neutrophils release MMP-9, which then exacerbates the damage.

"What we learn is that stroke is simply not a cerebral vascular event. It's a whole-body event. Both the brain and the body get signals that something's going on in the brain and as the immune system responds to try to help, it actually worsens the outcome. Therefore, by removing the blood and replacing it with the blood of those that have not experienced stroke, we get good outcomes."

Currently, blood-based therapies are emerging as treatments to combat aging and fight neurodegenerative diseases, the researchers noted.

Now, blood replacement therapy is a proven strategy that targets the pathological systemic responses to stroke, Ren said, and could reduce the mortality of stroke patients. "Blood indeed saves our brains and lives from stroke damage," she said. According to the Centers for Disease Control and Prevention, more than 795,000 Americans experience a stroke each year and 140,000 die from it.

"In an ideal circumstance, a person having a stroke would show up to Ruby (Memorial) or any hospital," Simpkins said. "They'd go through the proper protocol. We would remove their stroke blood and magically restore it with the right kind of blood that would tamp down this immune response they're experiencing. If it works out, that's good for all of us."

For patients or loved ones seeking information on current stroke trials, contact Simpkins at 304-293-7430.

Citation: 'Blood substitution therapy rescues the brain of mice from ischemic damage'

https://bit.ly/2YL5N1A

Long naps may be bad for health

Scientists show that drifting off for more than one hour could be risky

Sophia Antipolis, France - Many believe that lying down for a snooze is a harmless activity. But today, scientists show that drifting off for more than one hour could be risky. The study is presented at ESC Congress 2020.1

"Daytime napping is common all over the world and is generally considered a healthy habit," said study author Dr. Zhe Pan of Guangzhou Medical University, China. "A common view is that napping improves performance and counteracts the negative consequences of 'sleep debt'. Our study challenges these widely held opinions."

Previous research on the link between daytime naps and death or cardiovascular disease has produced conflicting results. In addition, it did not account for the duration of night-time sleep.

This study summarised the available evidence to assess the relationship between napping and the risks of all-cause death and cardiovascular disease. A total of 313,651 participants from more than 20 studies were included in the analysis. Some 39% of participants took naps.

The analysis found that long naps (more than 60 mins) were associated with a 30% greater risk of all-cause death and 34% higher likelihood of cardiovascular disease compared to no napping. When night-time sleep was taken into account, long naps were linked with an elevated risk of death only in those who slept more than six hours per night.

Overall, naps of any length were linked with a 19% elevated risk of death. The connection was more pronounced in women, who had a 22% greater likelihood of death with napping compared to no napping, and older participants, whose risk rose by 17% with naps.

Short naps (less than 60 minutes) were not risky for developing cardiovascular disease. Dr. Pan said: "The results suggest that shorter naps (especially those less than 30 to 45 minutes) might improve heart health in people who sleep insufficiently at night."

The reasons why napping affects the body are still uncertain, said Dr. Pan, but some studies have suggested that long snoozes are linked with higher levels of inflammation, which is risky for heart health and longevity.

Other research has connected napping with high blood pressure, diabetes, and poor overall physical health.

He concluded: "If you want to take a siesta, our study indicates it's safest to keep it under an hour. For those of us not in the habit of a daytime slumber, there is no convincing evidence to start."

Funding: None. Disclosures: The authors have no conflicts of interest.

References and notes *[1]Abstract title: The association between napping and the risk of cardiovascular disease and all-cause mortality: a systematic review and dose-response meta-analysis.*

https://wb.md/34PRbSr

Another Observational Trial Finds Famotidine Benefits Hospitalized COVID Patients

Significantly associated with a reduction in death and either death or intubation

Doug Brunk

Among hospitalized COVID-19 patients, the use of famotidine was significantly associated with a reduction in death and either death or intubation. It also demonstrated lower levels of serum markers for severe disease. The findings come from an observational study of 83 hospitalized patients that was published in the American Journal of Gastroenterology.

"The mechanism of exactly how famotidine works has yet to be proven," lead study author Jeffrey F. Mather, MS, said in an interview. "There's thought that it works directly on the virus, and there is thought that it works through inactivating certain proteases that are required for the virus infection, but I think the most interesting [hypothesis] is by Malone et al. "They're looking at the blocking of the histamine-2 receptor causing a decrease in the amount of histamine. It's all speculative, but it will be interesting if that gets worked out."

In a study that largely mimicked that of an earlier, larger published observational study on the topic (doi: 10.1053/j.gastro.2020.05.053), Mr. Mather and colleagues retrospectively evaluated 878 patients who tested positive for SARS-CoV-2 and who required admission to Hartford (Conn.) Hospital between Feb. 24, 2020, and May 14, 2020.

Patients were classified as receiving famotidine if they were treated with either oral or intravenous drug within 1 week of COVID-19 screening and/or hospital admission. Primary outcomes of interest were in-hospital death as recorded in the discharge of the patients, requirement for mechanical ventilation, and the composite of death or requirement for ventilation. Secondary outcomes of interest were several serum markers of disease activity including white blood cell count, lymphocyte count, and eosinophil count.

Famotidine was administered orally in 83% of the patients and intravenously in the remaining 17%. Mr. Mather, director of data management in the division of research management at Hartford Hospital, and his colleagues reported that 83 of the 878 patients studied (9.5%) received famotidine.

Compared with patients not treated with famotidine, those who received the drug were slightly younger (a mean of 64 vs. 68 years, respectively; *P* = .021); otherwise, there were no differences between the two groups in baseline demographics or in preexisting comorbidities.

The use of famotidine was associated with a decreased risk of in-hospital mortality (odds ratio, 0.37; *P* = .021) as well as combined death or intubation (OR, 0.47; *P* = .040). The outcomes were similar when the researchers performed propensity score matching to adjust for age differences between groups.

In addition, the use of famotidine was associated with lower levels of serum markers for severe disease including lower median peak C-reactive protein levels (9.4 vs. 12.7 mg/dL; *P* =. 002), lower median procalcitonin levels (0.16 vs. 0.30 ng/mL; *P* = .004), and a nonsignificant trend to lower median mean ferritin levels (797.5 vs. 964 ng/mL; *P* = .076).

Logistic regression analysis revealed that use of famotidine was an independent predictor of both lower mortality and combined death/intubation. In addition, predictors of both adverse outcomes included older age, a body mass index of greater than 30 kg/m^2, chronic kidney disease, the national early warning score, and a higher neutrophil-lymphocyte ratio.

"This is an important stepping stone, but until we have a randomized, controlled trial, we really can't speak about causation; we can only speak about association, and that's okay," Brennan Spiegel, MD, MSHS, director of health services research at Cedars-Sinai, Los Angeles, who was not affiliated with the study, said in an interview. "There's nothing wrong with association because finding associations can raise important hypotheses that can then be tested in prospective randomized trials, for example."

In July 2020, Dr. Spiegel and his colleagues published a separate paper looking at proton pump inhibitors and the risk of COVID-19. "In that study we did look at H_2 blockers, and we did find that they were slightly associated with a reduction in COVID-19," he said. "It was a small effect, but it was a benefit. When we see consistency among studies, it's a signal in the noise we can try and follow and see if there is something more to it."

Mr. Mather acknowledged certain limitations of the study, including the fact that patients who did and did not receive famotidine were propensity-matched for age.

"The risk factors that others have shown for adverse events are equivalent in the groups, but anytime you do a retrospective study like this there is the potential for underlying factors that may play a role in the outcomes that you're not considering," Mr. Mather said. "That's why the gold standard is the randomized trial, to wash those effects out. There's only an association here, and it supports the need for a randomized trial."

Famotidine is currently being tested in a double-blind randomized clinical trial in combination with either hydroxychloroquine or remdesivir (NCT 04370262).

"It's fascinating because famotidine is a safe medicine," added Dr. Spiegel, who is also co-editor in chief of the American Journal of Gastroenterology. "There are very few side effects; it's something we've been using for decades."

Mr. Mather and his colleagues reported having no financial disclosures. Dr. Spiegel disclosed that he has served on advisory boards for Allergan, Alnylam Pharmaceuticals, Arena Pharmaceuticals, Ironwood Pharmaceuticals, Salix Pharmaceuticals, Synergy Pharmaceuticals, and Takeda Pharmaceuticals.

https://bit.ly/31DVRZA

Puppy Preserved in Permafrost Ate a Chunk of One of Earth's Last Woolly Rhinos

Just before a tiny pup died during the last ice age, it ate a piece of meat from one of Earth's last woolly rhinos.

Laura Geggel, Live Science

Researchers made this discovery while doing a necropsy (an animal autopsy) on the mummified remains of the ice age puppy. After finding an undigested slab of skin with yellow fur in the puppy's stomach, researchers initially thought the puppy had chewed off a hunk of cave lion meat for its last meal.

But a DNA analysis of the slab revealed that it wasn't a cave lion (*Panthera spelaea*), but a woolly rhinoceros (*Coelodonta antiquitatis*), which went extinct around 14,000 years ago, right about the time that this pup had its last meal.

(© Sergej Fedorov)

That means this puppy ate one of the last woolly rhinos to ever exist, said Edana Lord, a doctoral student at the Centre for Palaeogenetics in Sweden, a joint venture between Stockholm University and the Swedish Museum of Natural History. Lord co-authored a study published August 13 in the journal *Current Biology* on the extinction of the woolly rhinos.

The mummified puppy was discovered in Tumat, a rural locality in northeastern Siberia, in 2011. An analysis revealed that the puppy was likely between 3 and 9 months old when it died, but it's unclear whether the pup was a dog or a wolf, Lord noted, a mystery that also surrounds an 18,000-year-old puppy found in Siberia in 2018, Live Science previously reported.

"I think it falls around that critical point for the dog/wolf domestication," she told Live Science, adding that a research team in Copenhagen is trying to decipher whether the Tumat pup was domesticated or not.

Radiocarbon dating revealed that the Tumat puppy lived about 14,000 years ago. Researchers also radiocarbon dated the woolly rhino slab, to rule out the possibility that the rhino hadn't died earlier and been preserved in Siberia's permafrost, only to be discovered by the puppy at a later date.

It's possible "that this puppy may have been one of a scavenging pack, and that the wolves either took down the rhino, or were looking for food and came across a rhino carcass," Lord noted.

If the puppy was domesticated, it's possible that it was living with humans, who may have shared the rhino meal with the pup, she said.

Soon after the puppy ate the woolly rhino, it died, although it's anyone's guess how.

The researchers were able to rule out one scenario, though; "It doesn't look like it's been squashed," before it was preserved as a mummy in the cold permafrost, Lord said.

Despite this "rhino dinner," predators probably didn't cause the extinction of the woolly rhino, according to Lord's new research. Instead, the culprit was the rapidly warming climate at the end of the last ice age, she and her colleagues found.

When the team sequenced a woolly rhinoceros nuclear genome and 14 mitochondrial genomes (DNA passed down the maternal line) - including the specimen found in the pup's belly - they found that the woolly rhino population was stable and diverse up until a few thousands years before the herbivores went extinct.

This genetic diversity indicates that there wasn't inbreeding, a problem that plagued the dwarf woolly mammoths on Wrangel Island off the northern coast of Russia about 4,000 years ago.

Because of the genetic diversity, as well as "the association of the extinction with the Bølling-Allerød interstadial, a very abrupt warming period [about 14,700 to 12,900 years ago], we suggest that

the woolly rhinoceros went extinct due to climate change," Lord said.

The DNA analyses also revealed that the woolly rhinoceros had genetic mutations that helped it adapt to cold weather.

One such mutation made the woolly creature less sensitive to feeling the cold, "which means that they would have been able to survive better in the more extreme cold," Lord said. "Because of these genomic adaptations to Arctic climate, they probably weren't well adapted to deal with the warming climate."

Moreover, the the rhinos were accustomed to foraging in the dry grasslands, but the warming climate during the Bølling-Allerød interstadial changed their environment to a snowy, "wooded shrubby habitat," which didn't provide the "favorite food of the rhinos," Lord said.

Puppies, on the other hand, will eat nearly anything, from woolly rhinos to shoes, which might explain their adaptability.

https://bit.ly/3qD0ebz

UofSC researchers reveal how THC may treat acute respiratory distress syndrome

ARDS caused by Staphylococcal enterotoxin, can be completely prevented by treatment with Δ9-tetrahydrocannabinol

COLUMBIA, SC - Acute Respiratory Distress Syndrome (ARDS), when caused by a bacterial toxin known as Staphylococcal enterotoxin, can be completely prevented by treatment with Δ9-tetrahydrocannabinol (THC), a cannabinoid found in the cannabis plant. This exciting finding, recently published in the highly cited *British Journal of Pharmacology*, also suggests a possible treatment for ARDS caused by COVID-19.

This new paper is based on research studies from the laboratories of Dr. Mitzi Nagarkatti and Dr. Prakash Nagarkatti at the University of South Carolina (UofSC) School of Medicine, Department of Pathology, Microbiology and Immunology. The Nagarkattis published "Protective Effects of Δ9-Tetrahydrocannabinol Against Enterotoxin-induced Acute Respiratory Distress Syndrome is Mediated by Modulation of Microbiota," with co-authors Amira Mohammed, Hasan Alghetaa and Juhua Zhou, who also work in their UofSC School of Medicine laboratories, and Saurabh Chatterjee from the UofSC Arnold School of Public Health. Drs. Mitzi and Prakash Nagarkatti have for years studied how plant-derived compounds can be used to prevent and reduce inflammation throughout the body.

The incidence of ARDS in the United States is 78.9 per 100,000 persons/year and the mortality rate is 38.5 percent. When inhaled, Staphylococcal enterotoxin can cause ARDS by activating immune cells to produce massive amounts of cytokines leading to "cytokine storm," which can cause the lungs and other organs to fail, often resulting in death. This immune process is similar to that seen in patients with severe COVID-19 who are admitted to the hospital and develop ARDS accompanied by cytokine storm, which leads to respiratory and multi-organ failure. These studies therefore raise the exciting possibility of using cannabinoids to treat ARDS seen in COVID-19 patients.

These studies also showed that Staphylococcal enterotoxin alters the microbiome in the lungs leading to the emergence of pathogenic microbiota. But THC helps this symptom too, by promoting beneficial bacteria that suppress inflammation thereby preventing the damage to the lungs.

"Acute respiratory distress syndrome is triggered by a variety of etiologic agents. Currently, there are no FDA-approved drugs to treat ARDS because of which the mortality rate is close to 40 percent. Our studies suggest that THC is highly effective to treat ARDS and thus, clinical trials are critical to investigate if this works," said Mitzi Nagarkatti.

"Cytokine storm is a huge clinical issue which leads to multiorgan failure and often death. It is also seen in COVID-19 patients, and there are no effective treatment modalities against this syndrome. We have been working on cannabinoids for over 20 years and found that cannabinoids such as THC are highly anti-inflammatory. Thus, our studies raise the exciting suggestion to test THC against ARDS seen in COVID-19 patients," said Prakash Nagarkatti.

The Nagarkatti laboratory has performed decades of pioneering studies on cannabinoids. In fact, their studies on the use of another cannabinoid derived from the cannabis plant, cannabidiol (CBD), to treat autoimmune hepatitis have been well-recognized in the field and have led to FDA approval of CBD as an orphan drug to treat this disorder.

The Nagarkatti Laboratory has published extensively to demonstrate that cannabinoids are potent anti-inflammatory agents that can be used safely to treat a variety of inflammatory and autoimmune diseases such as multiple sclerosis, colitis, hepatitis and the like.

These studies were supported in part by National Institutes of Health grants: P01AT003961, P20GM103641, R01AT006888, R01ES030144, R01AI123947, R01AI129788 awarded to M. Nagarkatti and P. Nagarkatti. Amira Mohammed received a fellowship from the Ministry of Higher Education and Scientific Research (MOHESR), Iraq.

https://bit.ly/31Ef8Kt

A Man Lost His Hearing And Suffered Inflamed Eyes After Getting a Standard Back Tattoo

Getting inked isn't without its share of risks.

Mike McRae

Getting inked isn't without its share of risks. We're not just talking regrets over your ex's name either – there's the slim chance of an allergic reaction, possibility of infection, and even the potential you'll hide warning signs of cancer.

Thankfully, hearing loss, lung lesions, and eye inflammation aren't usually concerns for the freshly tattooed. But when specialists at Fukuoka University Hospital in Japan encountered these symptoms in a 35-year-old male patient, they were able to link them back to his recent art piece.

Tattoos were probably the furthest thing from the patient's mind when he presented to the Department of Ophthalmology after suffering abnormal vision for the past four months.

Doctors diagnosed the man with an inflammatory condition called uveitis, which gets its name because it affects the middle layer of tissue in the eye's wall called the uvea.

Without any obvious signs of trauma or infection that could be blamed for the condition, medical specialists suspected that accumulations of inflammatory cells called granulomas might be behind the swelling and redness.

The condition itself is referred to as sarcoidosis. Although it's associated with an immune response, its trigger isn't always obvious.

Sure enough, blood tests showed elevated levels of the sorts of hormones expected in an immune response. A CT scan of the patient's chest also revealed a bunch of tiny nodules, another feature common in cases of sarcoidosis.

Shortly after receiving treatment, the man came down with yet another symptom – a loss of hearing in both ears.

Though not overly common, a quick look through the literature reveals cases where those granuloma parties can accumulate around nerves in the skull and around the face, interfering with hearing.

Fortunately a couple of weeks on corticosteroids did the trick, clearing up not just the eye inflammation but returning the patient's hearing.

As to the cause, while investigating his symptoms the doctors took a close look at the six-month-old tattoo on the man's back.

They found signs of granulomas in the skin eruptions within the tattoo's inked lines. It's not uncommon to find these painless lesions popping up as a reaction to the metals in certain inks, especially months following injection.

It's probably not all that surprising that tattoos can occasionally trigger reactions in hypersensitive individuals. In recent years we've learned more about how white blood cells are the caretakers of the ink, going as far as passing it down through the generations.

With the immune system playing such a central role in maintaining a tattoo, there's bound to be cases where biology goes a little astray.

Luckily the course of corticosteroids cleared up the patient's tattoo granulomas too, leaving him with skin as clear as his hearing.

In this case, the link between the back tattoo and sarcoidosis isn't confirmed beyond all doubt. Nonetheless, the authors advise signs of granulomas in relatively recent ink should be a reason to look for signs of inflammation elsewhere in the body.

Just one more thing to keep in mind when getting your partner's name inked into your back.

This research was published in *BMJ Case Reports*.

https://go.nature.com/34NNLQ4

The mosquito strategy that could eliminate dengue

Infecting the insects with a bacterium to stop disease transmission produces 'staggering' reduction in cases.

Ewen Callaway

Epidemiologists typically speak in qualified and caveated language. But newly released results from a trial of a biological technology that aims to stop the spread of mosquito-borne diseases have them using terms such as "staggering" and "epochal". The study, conducted in an Indonesia city, showed that releasing mosquitoes modified to carry a bacterium called *Wolbachia*, which stops the insects from transmitting some viruses, led to a steep drop in cases of dengue fever. The findings provide the strongest evidence yet that the technique, in development since the 1990s, could rid the world of some of these deadly diseases, researchers say.

The trial in Yogyakarta released *Wolbachia*-infected mosquitoes into randomly designated portions of the metropolis. Rates of dengue in these places were 77% lower, over several years, compared with areas that did not receive the mosquitoes. The results were reported in press releases on 26 August, but the full data underlying the figures are yet to be published.

It will be important to scrutinize the full data, but "a 77% reduction is really extraordinary", says Philip McCall, a vector biologist at the Liverpool School of Tropical Medicine, UK. "This does have huge promise."

The study has been running since 2016 and finished several months early because of COVID-19. But scientists say the results should support roll-out of the technology worldwide. The trial was coordinated by the non-profit World Mosquito Program (WMP), which hopes to deploy the mosquitoes to dengue-endemic areas all over the world.

"This a real breakthrough, a new hope for us, for the people and hopefully for the programme," says Adi Utarini, a public health researcher at University of Gadjah Mada in Indonesia, who co-led the trial.

Stopping transmission

The approach proven in the Yogyakarta trial was pioneered by a team led by Scott O'Neill, a microbiologist at the University of Monash in Melbourne, Australia, and director of the WMP. Around 60% of insect species carry *Wolbachia pipientis*, but the bacteria do not naturally infect the *Aedes aegypti* mosquito species that transmits dengue, Zika and numerous other viruses. Beginning in the 1990s, O'Neill's team developed laboratory populations of infected *A. aegypti* and showed these insects do not transmit viruses including dengue.

The team first began releasing the mosquitoes in parts of northeastern Australia that experienced periodic outbreaks of dengue — a disease that infects nearly 400 million people annually and kills 25,000, mostly in low- and middle-income countries in Asia, the Pacific and Latin America. The bacteria tend to quickly spread throughout local mosquito populations, and a 2018 study of a release programme in Townsville found that dengue rates plummeted after 4 million mosquitoes were released in different neighbourhoods. But the study did not include control areas that did not have mosquito releases. Australian outbreaks of dengue are also smaller and less frequent than those that hit cities in Southeast Asia and Latin America, where the virus is endemic.

The WMP launched the Yogyakarta trial to fill those gaps. Utarini and her colleagues divided the city of nearly 400,000 people into 24 clusters, and randomly selected 12 for mosquito release and 12 to serve as controls. Working with clinics scattered about Yogyakarta, the researchers identified 400 confirmed cases of dengue among thousands of people who showed up with acute fevers. They then compared where people with dengue — who were mostly children — had been in the previous two weeks, to determine whether they had been in an area where mosquitoes had been released or not.

The data from the trial were unblinded in June — a few months earlier than scheduled, because of rising coronavirus cases in Indonesia. But they were "pretty staggering", says Nicholas Jewell, a biostatistician at the London School of Hygiene and Tropical Medicine (LSHTM) and the University of California, , Berkeley, who co-led the study. The 77% reduction in dengue cases in areas that received *Wolbachia* mosquitoes translates to people being 4 times less likely to develop the disease.

"I've never been involved in a study quite as successful as this," says Jewell, who has studied infectious disease interventions since the start of the HIV epidemic in the 1980s. "We've never had anything like this. Condoms provide this level of protection," he adds. Jewell reckons that their estimate for the reduction in dengue cases is conservative, because many people probably moved between areas with *Wolbachia* mosquitoes and without. (Now that the trial has finished done, the WMP will release modified mosquito across the entire city. "That's our obligation," says Utarini.)

With the underlying data unpublished, McCall says that many questions remain unanswered, such as how the level of protection varied between different areas, and how this relates to the prevalence of *Wolbachia* in local populations. "All we have is that golden number. We need to hear a lot more about it," he says.

The fall in dengue rates "provides strong evidence supporting the use of Wolbachia", says Neal Alexander, an epidemiologist at LSHTM. Looking at how people's mobility between treated and untreated areas influenced protection should help to determine how generalizable the releases are to other places.

Next decade

"Scale-up" is what O'Neill plans to do next. The WMP hopes to release *Wolbachia* mosquitoes in areas covering 75 million people at risk of dengue in the next 5 years and reach half a billion people in a decade. The releases have been done with regulatory approval and extensive local consultation, which will also need to be scaled up. One hurdle will be gaining the endorsement of the World Health Organization, which guides many countries' public-health decisions.

Another will be funding. Charities such as the Bill & Melinda Gates Foundation in Seattle, Washington (of which WMP is a part), Wellcome in London and Indonesia's Tahija Foundation have supported trials so far. But O'Neill says funding from governments and bodies such as the World Bank and Inter-American Development Bank will be needed to help finance large-scale

releases. Work by independent economists has suggested that the mosquito releases, which are estimated to cost between around US$12 to $21 per person covered, pay for themselves within a few years by reducing healthcare costs, lost income and other tolls of dengue.

The WHO ordinarily requires data from two separate trials to recommend an intervention, says Immo Kleinshmidt, an epidemiologist at LSHTM who was part of an independent board monitoring the trial. “But I suspect that the demand for this intervention from dengue-endemic countries will result in widespread introduction of this method, with a good prospect of eventually eliminating the disease,” he says. “The significance of this result is epochal.”

doi: 10.1038/d41586-020-02492-1

https://bit.ly/3bbDGxy

Japanese sake: the new pick-me-up? Yeast strain makes fatigue-fighting ornithine

Researchers found that a mutant strain of sake yeast produces high levels of the amino acid ornithine

Nara, Japan - Fans of sake, the traditional Japanese alcoholic beverage, may have even more reason to enjoy it now: Japanese scientists have discovered that a mutant strain of sake yeast produces high levels of the amino acid ornithine.

In a study published this month in *Metabolic Engineering*, researchers from the Nara Institute of Science and Technology and the Nara Prefecture Institute of Industrial Development have revealed that a mutant strain of sake yeast produces 10 times the amount of the amino acid ornithine compared with the parent yeast strain.

Ornithine is a non-protein-making amino acid and a precursor to two amino acids - arginine and proline. It has been found to perform several physiological functions, such as reducing fatigue and improving sleep quality.

"We wanted to obtain sake yeast strains with improved ethanol tolerance," says a first author of this article, Masataka Ohashi. "During sake fermentation, the yeast is exposed to high concentrations of ethanol, which impedes yeast cell growth, viability and fermentation. Increased ethanol tolerance in sake yeast strains could improve ethanol production and reduce fermentation time."

To find ethanol-tolerant yeast strains, the researchers isolated mutants that accumulated proline, which can alleviate ethanol toxicity, using a conventional mutagenesis (i.e., one that doesn't involve genetic modification). They also conducted whole genome sequencing analysis, and performed brewing tests with sake yeast strains. Then they identified and analyzed a new mutation in a gene that encodes a variant of *N*-acetyl glutamate kinase that increases intracellular ornithine level.

"We previously constructed self-cloning industrial yeast strains that accumulate proline to increase ethanol tolerance and productivity of yeast," explains Prof. Hiroshi Takagi, a corresponding author. "But those yeasts have not been yet acceptable to consumers because they're considered to be genetically modified, even though a self-cloning yeast has no foreign genes or DNA sequences - they only have yeast DNA."

The researchers successfully isolated non-genetically modified yeasts that produced 10 times the amount of ornithine compared with the parent strain, which is widely used in Japanese sake breweries, and the sake brewed with them contained 4-5 times more ornithine.

The results of this study will contribute to the development of improved yeast strains for production of high levels of ornithine, and the strain obtained in this study could be readily applied to sake,

wine, and beer brewing. Ornithine-accumulating yeast strains could also be used in the production of ornithine-rich dietary supplements made from these yeasts and their products.

Prof. Takagi also describes "There are two major purposes for breeding of industrial yeast: improvement of fermentation ability with enhanced tolerance to environmental stresses during fermentation processes and diversity of product taste and flavor with modified metabolic pathways. In yeast, amino acid metabolisms vary under different growth environments and the metabolic styles form a complicated but robust network. The elucidation of metabolic regulatory mechanisms and physiological roles for amino acids is important fundamental research for understanding life phenomenon. The yeast is reliable and safe in food production, and thus the development of novel strains that overproduce 'functional amino acids' such as ornithine, proline and branched-amino acids, would greatly contribute to food-related industries."

Resource

Title: High-level production of ornithine by expression of the feedback inhibition-insensitive N-acetyl glutamate kinase in the sake yeast Saccharomyces cerevisiae
Authors: Masataka Ohashi, Ryo Nasuno, Shota Isogai & Hiroshi Takagi
Journal: Metabolic Engineering DOI: 10.1016/j.ymben.2020.08.005

https://bit.ly/3jrz9tQ

Antiviral used to treat cat coronavirus also works against SARS-CoV-2

New study showing that a drug that cures deadly peritonitis in cats also works well enough against SARS-CoV-2 to fast-track it into human clinical trials.

Researchers at the University of Alberta are preparing to launch clinical trials of a drug used to cure a deadly disease caused by a coronavirus in cats that they expect will also be effective as a treatment for humans against COVID-19.

"In just two months, our results have shown that the drug is effective at inhibiting viral replication in cells with SARS-CoV-2," said Joanne Lemieux, a professor of biochemistry in the Faculty of Medicine & Dentistry.

"This drug is very likely to work in humans, so we're encouraged that it will be an effective antiviral treatment for COVID-19 patients."

The drug is a protease inhibitor that interferes with the virus's ability to replicate, thus ending an infection.

Proteases are key to many body functions and are common targets for drugs to treat everything from high blood pressure to cancer and HIV.

First studied by U of A chemist John Vederas and biochemist Michael James following the 2003 outbreak of severe acute respiratory syndrome (SARS), the protease inhibitor was further developed by veterinary researchers who showed it cures a disease that is fatal in cats.

The work to test the drug against the coronavirus that causes COVID-19 was a co-operative effort between four U of A laboratories, run by Lemieux, Vederas, biochemistry professor Howard Young and the founding director of the Li Ka Shing Institute of Virology, Lorne Tyrrell.

Some of the experiments were carried out by the Stanford Synchrotron Radiation Lightsource Structural Molecular Biology program.

Their findings were published today in the peer-reviewed journal *Nature Communications* after first being posted on BioRxIV, a research website.

"There's a rule with COVID research that all results need to be made public immediately," Lemieux said, which is why they were posted before being peer-reviewed.

She said interest in the work is high, with the paper being accessed thousands of times as soon as it was posted.

Lemieux explained that Vederas synthesized the compounds, and Tyrrell tested them against the SARS-CoV-2 virus in test tubes and in human cell lines.

The Young and Lemieux groups then revealed the crystal structure of the drug as it binds with the protein.

"We determined the three-dimensional shape of the protease with the drug in the active site pocket, showing the mechanism of inhibition," she said. "This will allow us to develop even more effective drugs."

Lemieux said she will continue to test modifications of the inhibitor to make it an even better fit inside the virus. But she said the current drug shows enough antiviral action against SARS-CoV-2 to proceed immediately to clinical trials.

"Typically for a drug to go into clinical trials, it has to be confirmed in the lab and then tested in animal models," Lemieux said. "Because this drug has already been used to treat cats with coronavirus, and it's effective with little to no toxicity, it's already passed those stages and this allows us to move forward."

"Because of the strong data that we and others have gathered we're pursuing clinical trials for this drug as an antiviral for COVID-19."

The researchers have established a collaboration with Anivive Life Sciences, a veterinary medicine company that is developing the drug for cats, to produce the quality and quantity of drug needed for human clinical trials.

Lemieux said it will likely be tested in Alberta in combination with other promising antivirals such as remdesivir, the first treatment approved for conditional use in some countries including the United States and Canada.

The U of A researchers' work was funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, Alberta Innovates, Li Ka Shing Institute of Virology and the GSK Chair in Virology.

https://bbc.in/32EiDQu

Elon Musk to show off working brain-hacking device

Elon Musk is due to demonstrate a working brain-to-machine interface as part of his ambitious plans to give people superhuman powers.

His brain-hacking company, Neuralink, applied to start human trials last year. But Friday's demonstration will involve a robot and "neurons firing in real time", a series of tweets reveals.

The interface could allow people with neurological conditions to control phones or computers with their mind. But the long-term ambition is to usher in an age of what Mr Musk calls "superhuman cognition". People need to merge with artificial intelligence, he says, in part to avoid a scenario where AI becomes so powerful it destroys the human race.

Founded in 2017, Neuralink has worked hard to recruit scientists, something Mr Musk was still advertising for on Twitter last month.

The device the company is developing consists of a tiny probe containing more than 3,000 electrodes attached to flexible threads thinner than a human hair, which can monitor the activity of 1,000 brain neurons.

In its last update, more than a year ago, the company said it had carried out tests on a monkey that had been able to control a computer with its brain. It has also built a "neurosurgical robot" that it says can insert 192 electrodes into the brain every minute.

University of Pittsburgh assistant professor of physical medicine and rehabilitation Jennifer Collinger described what Mr Musk was trying to do as "truly disruptive technology in a difficult space of medical technology".

"Neuralink has significant resources and critically a team of scientists, engineers and clinicians working towards a common goal, which gives them a great chance of success," she said. But she added: "Even with these resources, medical-device development

takes time and safety needs to be a top priority, so I suspect the process may take longer than they have stated as their goals."

Ari Benjamin, at the University of Pennsylvania's Kording Lab, told BBC News the real stumbling block for the technology could be the sheer complexity of the human brain.

"Once they have the recordings, Neuralink will need to decode them and will someday hit the barrier that is our lack of basic understanding of how the brain works, no matter how many neurons they record from. "Decoding goals and movement plans is hard when you don't understand the neural code in which those things are communicated."

Mr Musk's companies SpaceX and Tesla have captured the public imagination with his attempts to drive progress in spaceflight and electric vehicles respectively. But both also demonstrate the entrepreneur's habit of making bold declarations about projects that end up taking much longer to complete than planned.

https://bit.ly/2YQSOeR

Here's how the U.S. could release a COVID-19 vaccine before the election—and why that scares some

Trump promises to deliver a COVID-19 vaccine would succeed "before the end of the year, or maybe even sooner."
That promise concerns many vaccine veterans.

By Jon Cohen

When President Donald Trump accepted his party's nomination for another term last night at the Republican National Convention, he pledged that the push by his administration's Operation Warp Speed to deliver a COVID-19 vaccine would succeed "before the end of the year, or maybe even sooner."

That promise concerns many vaccine veterans. They worry that political forces—the U.S. presidential election on 3 November, nationalistic pride to "win" a race, the need to resuscitate economies—could lead to premature and dangerous approvals under mechanisms such as the emergency use authorization (EUA), a pathway used by the U.S. Food and Drug Administration (FDA) to allow rapid access to diagnostics, treatments, and vaccines. Long a bastion of regulatory rigor that many other countries look to for guidance, FDA has been criticized for issuing EUAs for two COVID-19 treatments, convalescent plasma and hydroxychloroquine, based on scant data and apparent political pressure. (The hydroxychloroquine EUA has since been revoked.) Paul Offit, a pediatrician at the Children's Hospital of Philadelphia who is a member of a group that advises FDA about its vaccine decisions, suspects the Trump administration might seek a COVID-19 vaccine EUA before the elections and say: "We Warp Speeded our way to a vaccine."

China and Russia already have approved limited use of COVID-19 vaccines outside of clinical trials, offering baffling—and sharply criticized—rationales. In the United States, Operation Warp Speed, as its name implies, hopes to move vaccine candidates forward more quickly than ever before. It has invested more than $10 billion in developing eight different COVID-19 vaccines, with much of that money pre-purchasing hundreds of millions of doses so they will be at the ready if an FDA approval comes through. Three of the Warp Speed-backed vaccines have entered efficacy trials, and one manufacturer has pledged to start delivering the first of 300 million doses as early as October—though one person close to Operation Warp Speed says, "There won't be enough vaccine in October to create anything other than a news story."

FDA officials have insisted they have "unwavering regulatory safeguards" and will not cut any corners. "The acceleration is really around taking financial risk [with regard to] the development process," FDA Commissioner Stephen Hahn said at a U.S. House of Representatives committee hearing about the country's COVID-

19 response in June. "We will rely upon data and science when it comes to that decision about an EUA."

Peter Marks, who runs the FDA division that oversees vaccine approval, has vowed that he would resign if the Trump administration pushed through a vaccine that was not clearly safe and effective. And he insists that FDA will consult with the Vaccine and Related Biological Products Advisory Committee (VRBPAC), which Offit sits on, to publicly discuss data related to any approval request. "Approval should be something that we can make transparent, and to do anything less than that is really a disservice to people," Marks says. VRBPAC's next meeting is scheduled for 22 October, 12 days before the presidential and congressional elections.

Science spoke with a range of researchers and regulators about how a COVID-19 vaccine approval might be accelerated and the potential consequences.

What's the traditional vaccine approval pathway?

After initial laboratory and animal tests, vaccines enter phase I human trials that typically have about 20 to 100 people and primarily analyze safety and immune responses. Phase II studies are larger versions of phase I trials. Phase III studies attempt to determine whether a vaccine works by comparing people who receive it with those who are given a placebo shot and, over several months or years, seeing how many in each group get infected. For COVID-19 vaccines these trials involve anywhere from 10,000 to 60,000 people and will need a total of about 150 cases of disease to determine whether a candidate works. Once the trial endpoints are met, a vaccine developer seeking FDA approval would file a biologics license application; VRBPAC would review the data at a public meeting, then vote on whether the vaccine should receive approval—a recommendation FDA normally follows. The approval process, which involves inspecting the vaccine's manufacturing plants, can often take 1 year.

How does an EUA work?

An EUA in the United States, and similar regulatory pathways in many countries, allows use of an unlicensed vaccine outside of a clinical trial. The EUA could stipulate the use of the vaccine in a limited population, for example, health care workers or the elderly. Or it could be for the general population. An EUA offers liability protections to vaccinemakers, and it remains in effect as long as there is a public health, military, or national security emergency. When the emergency ends, so does the approval.

What safety and efficacy evidence would FDA require before issuing an EUA?

FDA issued a "guidance for industry" in June that says any emergency decision on a COVID-19 vaccine would be based on factors such as "the target population, the characteristics of the product, [and] the preclinical and human clinical study data." The guidance specifies that FDA will only approve an EUA for a vaccine that has at least 50% efficacy. But estimates of efficacy have error bars of sorts; for a COVID-19 vaccine, FDA wants 95% confidence that efficacy is no lower than 30%. The decision to consider an EUA request would likely be based on data reviewed by the independent boards, set up by the vaccine's sponsors or clinical trial investigators, that monitor safety and efficacy during the study.

What harm could an EUA do?

Public Citizen, a public advocacy group, has argued that regardless of whether a COVID-19 vaccine is effective, an EUA could fuel existing vaccine hesitancy. "The 'logic' of saving several months by a faster but riskier EUA pathway will surely be outweighed by the loss in public confidence in the vaccine, accompanied by decreased willingness to be vaccinated," Public Citizen warned in a

6 August letter to Marks and his superiors. An EUA for a vaccine might also make it more difficult to recruit people for clinical trials of that vaccine and others, because participants might not want to take the risk of receiving a placebo when they can get a shot of a product that's authorized for use.

What if the vaccine doesn't work well or causes harm?

Vaccines go into healthy people, so putting them into use before fully assessing their risks and benefits is a bigger gamble than issuing an EUA for an experimental treatment for someone already ill. If a hastily approved COVID-19 vaccine candidate proves ineffective or has serious side effects, confidence in what many see as the best hope to ending the pandemic could plummet. The Solidarity Vaccines Trials Expert Group of the World Health Organization (WHO) argued in an editorial published in *The Lancet* yesterday that a weakly effective vaccine could actually worsen the pandemic if it induced authorities to relax control measures, such as mask wearing, or if vaccinated people believed they were immune and increased their risk-taking behavior.

Has an EUA ever been used for a vaccine?

Yes. In 2005 FDA granted an EUA for an anthrax vaccine for people who the military determined were at high risk of attack from anthrax used as a biological weapon. The episode provoked lawsuits claiming there was no evidence that the vaccine, which the military required soldiers to get, worked against the type of inhalational anthrax used in bioweapons. A judge ruled in favor of the plaintiffs, but by then the vaccine had become voluntary.

What's the difference between FDA's expanded access program and an EUA?

Typically expanded access, also called compassionate use, covers treatments, not vaccines, in the United States. It's for individuals who have a life-threatening condition and no alternatives or for small groups of sick people when a treatment has promising evidence but efficacy has not been proven yet. Anyone who receives the experimental medicine signs an informed consent form, and institutions that provide it have to seek permission from FDA, submit a protocol, report adverse events, and do continued safety monitoring. An EUA eliminates these requirements. FDA allowed nearly 100,000 people to receive convalescent plasma through expanded access—an unusually large instance of compassionate use—but last week granted an EUA that proponents said would cut paperwork. The Democratic Republic of the Congo used its own expanded access regulation to allow more than 300,000 people to use an unlicensed Ebola vaccine.

Does Europe have a similar emergency approval process?

The European Medicines Agency (EMA) can issue "conditional approval" for a vaccine during a pandemic. Under a rolling-review process, companies continue submitting data as they becomes available. The United Kingdom, which will be leaving the EMA's authority because of Brexit, today issued a consultation for public comment on how its regulatory agency might issue its own temporary authorization of an unlicensed COVID-19 vaccine.

How did China and Russia speed approval of their COVID-19 vaccines?

China on 25 June gave CanSino a 1-year approval to use its COVID-19 vaccine in the Chinese military, although there is no evidence beyond statements by company officials that anyone has received it. On 22 July, China also allowed Sinopharm's China National Biotec Group Company to give its COVID-19 vaccine to health care workers, customs workers, and others in "high-risk" professions. Both vaccines are still in phase III efficacy trials. CanSino also reportedly is in discussion with regulators in Pakistan and unnamed Latin American countries about early approval of its vaccine.

Russia's Gamaleya Research Institute of Epidemiology and Microbiology in Moscow on 11 August received a "registration certificate" to give a COVID-19 vaccine to what a Ministry of Health spokesperson described as "a small number of citizens from vulnerable groups," including medical staff and the elderly. Dubbed Sputnik V, a clear reference to the U.S.-Soviet space race, the product is billed as "the first registered COVID-19 vaccine." The registration says it cannot be used widely until after 1 January 2021, but President Vladimir Putin said, "I hope we can start a massive release of this vaccine soon."

Many countries do not have strong regulatory agencies. How do they decide whether to use a COVID-19 vaccine that is not licensed?

WHO has what it calls an Emergency Use Listing, which many low- and middle-income countries have relied on in the past. "We can give a benefit/risk decision on a product and specify the conditions under which it should be used," says Emer Cooke, director of WHO's Regulation of Medicines and other Health Technologies. "We act like a regulatory body, but we're not a regulatory body." Cooke, who recently was elected to head EMA later this year, says their job is especially complex now because of the flood of COVID-19 vaccine candidates and the intense pressure to find one that is safe and effective. "I think we are seeing more political influences now than we would normally see," she says.

doi:10.1126/science.abe5150

https://bit.ly/34OU46a

A coffee and catnap keep you sharp on the nightshift

Unlikely combination can improve attention and reduce sleep inertia

A simple coffee and a quick catnap could be the cure for staying alert on the nightshift as new research from the University of South Australia shows that this unlikely combination can improve attention and reduce sleep inertia.

In Australia, more than 1.4 million people are employed in shift work, with more than 200,000 regularly working night or evening shifts.

Lead researcher, Dr Stephanie Centofanti from UniSA Online and the Sleep and Chronobiology Laboratory at UniSA says the finding could help counteract the kind of sleep inertia that is experienced by many shiftworkers.

"Shift workers are often chronically sleep-deprived because they have disrupted and irregular sleep patterns," Dr Centofanti says.

"As a result, they commonly use a range of strategies to try to boost their alertness while on the nightshift, and these can include taking power naps and drinking coffee - yet it's important to understand that there are disadvantages for both.

"Many workers nap during a night shift because they get so tired. But the downside is that they can experience 'sleep inertia' - that grogginess you have just after you wake up - and this can impair their performance and mood for up to an hour after their nap.

"Caffeine is also used by many people to stay awake and alert. But again, if you have too much coffee it can harm your overall sleep and health. And, if you use it to perk you up after a nap, it can take a good 20-30 minutes to kick in, so there's a significant time delay before you feel the desired effect.

"A 'caffeine-nap' (or 'caff-nap') could be a viable alternative - by drinking a coffee before taking a nap, shiftworkers can gain the benefits of a 20-30-minute nap then the perk of the caffeine when they wake. It's a win-win."

The small pilot study tested the impact of 200 mg of caffeine (equivalent to 1-2 regular cups of coffee) consumed by participants just before a 3.30am 30-minute nap, comparing results with a group that took a placebo.

Participants taking a 'caffeine-nap' showed marked improvements in both performance and alertness, indicating the potential of a 'caffeine-nap' to counteract sleep grogginess.

Dr Centofanti says this shows a promising fatigue countermeasure for shift workers. She says the next move is to test the new finding on more people.

https://bit.ly/2EIWqc3

China has 600 outposts across the world to recruit scientists

To recruit foreign experts and scientists in order to acquire advanced technology and protected intellectual property

By Rebecca Trager

The Chinese government has built a network of 600 international outposts across the world to recruit foreign experts and scientists in order to acquire advanced technology and protected intellectual property, the Australian Strategic Policy Institute (ASPI) has claimed. These talent recruitment programmes have been extremely successful, getting almost 60,000 overseas professionals to sign up between 2008 and 2016, according to China's own statistics.

In a new report, the ASPI, a thinktank founded by Australia's government, has created a database of 600 overseas talent-recruitment stations to illustrate the international reach of the Chinese Communist Party (CCP). The outposts are contracted out to organisations or individuals who are paid to recruit overseas scientists, and they might have no clear physical presence or be co-located with the organisations contracted to run them, the ASPI explained.

These stations are a growing part of China's talent-recruitment infrastructure, which includes the 'Thousand Talents' plan, the report, which was part funded by the US State Department, noted. The outposts may receive instructions to target individuals with access to particular technologies, or be paid up to A$30,000 (£16,400) annually plus bonus payments for each successful recruitment.

Unsurprisingly, the US is the main country targeted, with 146 of the 600 stations located there. The second highest number are in Germany and Australia, each with 57, followed by the UK with 49. Other outposts are found in Canada, Japan, France and Singapore. 'In addition to the US, it's likely that more than a thousand individuals have been recruited from each of the UK, Germany, Singapore, Canada, Japan, France and Australia since 2008,' the report concluded.

Texas investigation

In the US, for example, the ASPI cited an investigation by Texas A&M University system that found more than 100 staff were linked to China's talent recruitment programmes, only five of which had disclosed the connection despite a requirement to do so. That level of misconduct hasn't been reported in other countries, the thinktank said.

On 24 August the US Department of Justice (DOJ) announced the arrest of Texas A&M chemical engineering professor Zhengdong Cheng on allegations of obscuring his affiliations and collaborations with a Chinese university – Guangdong University of Technology – and at least one Chinese-owned company. Cheng led a team conducting research for Nasa, and the terms of his grant prohibited his participation or collaboration with China or any Chinese-owned company or university, the DOJ explained.

According to the criminal complaint, Cheng aimed to personally enrich himself by more than $86,000 (£64,000) in Nasa grant funds, gain access to the unique resources of the International Space Station, leverage Nasa grant resources to further the research of Chinese institutions and become a Thousand Talents participant. To do this he had to hide his affiliations with the Chinese government and private Chinese companies from Texas A&M, as well as Nasa.

'China is building an economy and academic institutions with bricks stolen from others all around the world,' said Ryan Patrick, US Attorney for the Southern District of Texas. 'While 1.4 million foreign researchers and academics are here in the US for the right reasons, the Chinese talents programme exploits our open and free universities,' he added. Patrick said these conflicts must be disclosed by academics when they exist, and warned that the DOJ will 'hold those accountable' when such conflict violates the law.

Divestment

The ASPI report advised governments around the world to, among other things, ensure that recipients of government research funding are required to disclose participation in foreign talent-recruitment programmes. The organisation also urged governments to establish a public database of all external funding received by public universities and their employees, and require universities to submit and update such data.

Among the ASPI's other recommendations are that research institutions worldwide carry out a comprehensive and independent audit of staff participation in Chinese talent-recruitment programmes, and strengthen existing staff travel databases to automatically flag conflicts with grant commitments and contracts. Its report further suggested that participants in such Chinese plans should be required to submit their contracts with the foreign institution and fully disclose any remuneration.

Meanwhile, the US State Department is advising US colleges and universities to divest from Chinese holdings in their endowments, warning them in an 18 August letter to act before it's too late. 'The boards of US university endowments would be prudent to divest from People's Republic of China firms' stocks in the likely outcome that enhanced listing standards lead to a wholesale de-listing of PRC firms from US exchanges by the end of next year,' wrote Keith Krach, the agency's undersecretary for economic growth, energy and the environment.

Krach said government agencies are accelerating investigations at universities for illicit PRC funding of research, intellectual property theft and the recruitment of talent. He cited the indictment earlier this year of Charles Lieber, the former head of Harvard University's chemistry department.

Lieber was arrested in January for allegedly lying about his participation in the Thousand Talents programme where he was awarded $1.5 million to establish a research lab at Wuhan University, and failing to disclose being paid $2.25 million over three years. He was indicted in June, and faces up to five years in prison if convicted.

Krach also pointed to the case of long-time University of Arkansas professor Simon Saw-Teong Ang, who was indicted by a federal grand jury in July on 42 counts of wire fraud and two counts of passport fraud. This was in relation to his alleged failure to disclose his participation in the Thousand Talents plan while receiving Nasa funding. If convicted, he faces up to 20 years in prison for each wire fraud count and 10 years in prison for each passport fraud count.

https://wb.md/34ObAqU

Statins Linked to Reduced Mortality in COVID-19

Treatment with statins was associated with a reduced risk of a severe or fatal course of COVID-19 by 30%, a meta-analysis of four published studies has shown.

Megan Brooks

In the analysis that included almost 9000 COVID-19 patients, there was a significantly reduced risk for fatal or severe COVID-19 among patients who were users of statins compared with non-users (pooled hazard ratio [HR], 0.70; 95% CI, 0.53 - 0.94).

Based on the findings, "it may be time we shift our focus to statins as the potential therapeutic options in COVID-19 patients," authors Syed Shahzad Hasan, PhD, University of Huddersfield, UK, and Chia Siang Kow, MPharm, International Medical University, Kuala Lumpur, Malaysia, wrote in a joint emailed comment to *Medscape Medical News*. The study was published online August 11 in *The American Journal of Cardiology*.

Moderate to Good Quality Data

The analysis included four studies published up to July 27 of this year. Eligible studies included those with a cohort or case-control designs, enrolled patients with confirmed COVID-19, and had data available allowing comparison of the risk of severe illness and/or mortality among statin users vs non-users in adjusted analyses, the authors note.

The four studies — one of "moderate" quality and three of "good" quality — included a total of 8990 COVID-19 patients.

In the pooled analysis, there was a significantly reduced risk for fatal or severe COVID-19 with use of statins compared to non-use of statins (pooled HR, 0.70; 95% CI, 0.53 - 0.94).

Their findings also "discredited the suggestion of harms with the use of statins in COVID-19 patients," the authors conclude.

"Since our meta-analysis included a fairly large total number of COVID-19 patients from four studies in which three are large-scale studies that adjusted extensively for multiple potential confounding factors, the findings can be considered reliable," Hasan and Kow write in their article.

Based on the results, "moderate-to-high intensity statin therapy is likely to be beneficial" in patients with COVID-19, they told *Medscape Medical News*.

However, they caution that more data from prospective studies are needed to substantiate the findings and to determine the appropriate regimen for a statin in COVID-19 patients.

Reached for comment, Yibin Wang, PhD, of the David Geffen School of Medicine, University of California, Los Angeles, said, "This is a very simple meta-analysis from four published studies which consistently reported a protective or neutral effect of statin usage on mortality or severe complications in COVID-19 patients."

Although the scope of this meta-analysis was "quite limited, the conclusion was not unexpected, as most of the clinical analysis so far reported supports the benefits or safety of statin usage in COVID-19 patients," Wang told *Medscape Medical News*.

Nonetheless, Questions Remain.

While there is "almost no dispute" about the safety of continuing statin therapy in COVID-19 patients, it remains to be determined if statin therapy can be implemented as an adjuvant or independent therapy and a part of the standard care for COVID-19 patients regardless of their hyperlipidemia status, said Wang, who was not associated with Hasan's and Kow's research.

"While statin usage is associated with several beneficial effects such as anti-inflammation and cytoprotection, these effects are usually observed from long-term usage rather than short-term/acute administration. Therefore, prospective studies and randomized trials should be conducted to test the efficacy of stain usage for COVID-19 patients with mild to severe symptoms," he noted.

"Considering the excellent record of statins as a safe and cheap drug, it is certainly a worthwhile effort to consider its broad-based usage for COVID-19 in order to lower the overall death and severe complications," Wang concluded.

Guillermo Rodriguez-Nava, MD, Department of Internal Medicine, AMITA Health Saint Francis Hospital, Evanston, Illinois, is first author on one of the studies included in this meta-analysis.

The retrospective single-center study found slower progression to death associated with atorvastatin in older patients with COVID-19 admitted to the intensive care unit.

"Currently, there are hundreds of clinical trials evaluating a wide variety of pharmacological therapies for COVID-19. Unfortunately, these trials take time, and we are getting results in dribs and drabs," Rodriguez-Nava told *Medscape Medical News*.

"In the meantime, the best available evidence is observational, and COVID-19 treatment regiments will continue to evolve. Whether atorvastatin is effective against COVID-19 is still under investigation. Nevertheless, clinicians should consider at least continuing them in patients with COVID-19," he advised.

The study had no specific funding. Hasan, Kow, Wang and Rodriguez-Nava have disclosed no relationships relevant to this research.
Am J Cardiol. Published online August 11, 2020. Full text

https://bit.ly/3jrJy8S

Microbes Living Deep Below Earth's Surface Could Be Remnants of Ancient Life Forms

Analysis reveals evolutionary path to life in the dark of two major groups of subsurface microbes has been more curious than we expected

Carly Cassella

There's an enormous variety of life thriving deep beneath Earth's surface. A new analysis of two major groups of subsurface microbes has now revealed that their evolutionary path to life in the dark has been more curious than we expected.

In our planet's first 2 billion years of existence, there was no oxygen in the atmosphere. Once the air on our blue planet changed, not all life forms adapted, with many microbes retreating into less oxygenated parts of the planet.

Patescibacteria and DPANN are two ubiquitous groups of such subsurface microbes - bacteria and archaea, respectively - that appear to have very simple genomes. This has led many to suspect that without the ability to breathe oxygen, these microbes might need to rely on complex interactions with other organisms to supplement their simple lifestyles.

Now, it seems we may not be giving them enough credit. New research indicates that instead of having a symbiotic dependency on other major groups of organisms, most Patescibacteria and DPANN live as completely free cells. "These microbes [..] are really special, really exciting examples of the early evolution of life," says Ramunas Stepanauskas, who studies microbial biology and evolution at the Bigelow Laboratory for Ocean Sciences.

"They may be remnants of ancient forms of life that had been hiding and thriving in the Earth's subsurface for billions of years."

Previous work on Patescibacteria and DPANN has gathered a small number of examples near the surface of the Earth, and mainly in North America, but this new study goes deeper and wider than ever before, analysing nearly 5,000 individual microbial cells from 46 locations around the globe, including a mud volcano on the bottom of the Mediterranean Sea, hydrothermal vents in the Pacific, and gold mines in South Africa.

"Our single cell genomic and biophysical observations do not support the prevailing view that Patescibacteria and DPANN are dominated by symbionts," the authors write.

"Their divergent coding potential, small genomes, and small cell sizes may be a result of an ancestral, primitive energy metabolism that relies solely on [fermentation]."

Fermentation is one of the metabolic options living organisms have for breaking down glucose without the help of oxygen, and many life forms use fermentation for energy production, especially the microbes that don't breathe air at all.

However, using fermentation is less efficient than breathing - it produces only 2 ATP per glucose compared to 38 ATP per glucose with aerobic respiration - so this type of metabolism comes with the cost of putting organisms in the metabolic slow lane.

Patescibacteria and DPANN are just fine with that, however. Based on the new analysis, the two groups contain no trace of what's known as an electron transport chain, a metabolic process that makes energy by dumping electrons onto oxygen. Their relatively simple, potentially ancient survival tricks simply don't need it.

Genomic research and direct experimental tests on samples representing the two groups showed no evidence of respiration, and close examination of cell-to-cell links revealed most were on their own, not attached to hosts like some of their surface cousins.

The authors can't deny that some symbiotic relationships could have been shaken apart by human handling, but gentle mixing was attempted when sorting the cells.

Even if the team is underestimating cell-to-cell interactions, genomic analysis found no evidence of evolutionary enrichment from symbiotic relationships compared to other phyla.

Rather, genome content and lab analysis of cell physiology suggests these microbial groups contain few, if any, other ways of producing energy than fermentation.

"Our findings indicate that Patescibacteria and DPANN are ancient forms of life that may have never learned how to breathe," says Stepanauskas. "These two major branches of the evolutionary tree of life constitute a large portion of the total microbial diversity on the planet - and yet they lack some capabilities that are typically expected in every form of life."

The study was published in *Frontiers in Microbiology*.