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Lyme Disease Doesn't Have a Vaccine, But a Yearly Preventative Shot Shows Promise

Lyme PrEP, delivers a single anti-Lyme antibody directly to a person rather than triggering the patient's own immune system to make many antibodies

Mark Klempner, The Conversation

Lyme disease has become an insidious epidemic in the United States. Caused by bacteria transmitted by an infected tick bite, symptoms can include arthritis, cardiac and neurological problems if left untreated.

It is the most common tick-borne illness in the United States, and the Centers for Disease Control and Prevention estimates that around 300,000 people likely contract the disease each year.

Scientists, doctors and ecologists have worked for decades to slow the spread of Lyme and the blacklegged, or deer, ticks that carry the disease-causing bacteria. However, the ticks' range continues to expand. Today, over 50 percent of the American population lives in an area where these ticks are found.

The US Food and Drug Administration approved a vaccine against Lyme in 1998, but it was met by controversy and pulled from the market three years later. Efforts continue today to create a human vaccine as well as stop the spread of Lyme by other means, including using gene-editing to immunize mice that can transmit the bacteria to ticks, killing deer and using pesticides to control ticks.

My colleagues and I have been working on a different kind of prevention: a yearly injection. I am an infectious diseases physician-scientist and have been studying and working toward preventing Lyme disease for much of my career. I also oversee UMass Medical School's MassBiologics, the only nonprofit, FDA-licensed manufacturer of vaccines and biologics in the United States.

Our method, known as Lyme PrEP, delivers a single anti-Lyme antibody directly to a person rather than triggering the patient's own immune system to make many antibodies as vaccines do.

It is designed to be a seasonal shot that people can get once a year before tick season begins. We have published several peer-reviewed articles on this methodology, including its success in mice and nonhuman primates. Later this year, we are scheduled to begin our first human phase 1 trial.

A vaccine's cautionary tale

In 1998, the FDA approved a Lyme vaccine composed of protein antigens from the surface of the Lyme bacteria, *Borrelia burgdorferi*.

A vaccine works by introducing proteins from the disease-causing agent into the body to trigger the body's immune response, which includes making antibodies against bacterial proteins.

Antibodies have been used to prevent and treat infectious diseases for over a century. In the case of the Lyme vaccine it can take many months for the body to build up the necessary level of immunity to prevent infection. It also means that some of the antibodies induced by the vaccine can have "off-target" effects, or side effects.

The vaccine, known as LYMErix, largely reduced infections but was withdrawn from the market after three years because of limitations and controversy.

It needed to be administered by multiple injections over a year before immunity developed. Uncertainty about the length of immunity from the vaccine also raised questions of whether a booster shot would be regularly needed. Further, publicity about side effects such as arthritis, reported by some who had been vaccinated, contributed to its decline in popularity. Today, a French

biotech company, in collaboration with Pfizer, is attempting to develop a Lyme vaccine that is currently in clinical trials.

A different approach

Unlike a vaccine, Lyme PrEP uses a single human antibody, or blood protein, to kill the bacteria in the tick's gut while it takes its blood drink, before the bacteria can get into the human host.

Through our research, we realized that just one of the antibodies that the human body developed after multiple injections of the LymeRx vaccine was sufficient to prevent infection. So we identified which antibody led to immunity and tested it in animals where it proved 100 percent effective.

These animal studies show Lyme PrEP gives protection immediately upon injection, as it circulates through the blood. Unlike a vaccine which induces many antibodies that may not contribute to protection but can cause side effects, this approach uses a single, defined antibody, thus reducing the risk of side effects. Initial tests of a single injection of Lyme PrEP protected mice for several weeks.

Humans, however, need to be protected longer, likely for the nine-month season when over 90 percent of cases occur. We have developed the Lyme PrEP antibody to extend its protective effects to cover this amount of time. Yet, the actual duration of protection will have to be determined during clinical trials. Our goal for the phase 1 clinical trial later this year is to test for the treatment's safety and determine how long it lasts in the bloodstream in humans. For the phase 1 trial we want to avoid testing the Lyme PrEP antibody on volunteers who may have already been exposed to the Lyme bacteria and have developed responses to the bacteria that could confuse the results. For that reason, initial testing will take place in volunteers who have not been exposed to Lyme disease.

If all goes well, phase 1 clinical trials would be completed in 2021. The phase 2 trial to test for safety and efficacy in a small group of volunteers would follow and then be followed by a phase 3 trial to test the efficacy on many volunteers. We hope to complete these larger studies in late 2022 or 2023. The COVID-19 pandemic has put in sharp focus the need to prevent infections and the old adage, "An ounce of protection is worth a pound of cure."

Mark Klempner, Professor of Medicine and Executive Vice Chancellor for MassBiologics, University of Massachusetts Medical School.

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Artificial brains may need sleep too

States that resemble sleep-like cycles quell the instability that comes with uninterrupted self-learning in artificial analogs of brains

No one can say whether androids will dream of electric sheep, but they will almost certainly need periods of rest that offer benefits similar to those that sleep provides to living brains, according to new research from Los Alamos National Laboratory.

"We study spiking neural networks, which are systems that learn much as living brains do," said Los Alamos National Laboratory computer scientist Yijing Watkins. "We were fascinated by the prospect of training a neuromorphic processor in a manner analogous to how humans and other biological systems learn from their environment during childhood development."

Watkins and her research team found that the network simulations became unstable after continuous periods of unsupervised learning. When they exposed the networks to states that are analogous to the waves that living brains experience during sleep, stability was restored. "It was as though we were giving the neural networks the equivalent of a good night's rest," said Watkins.

The discovery came about as the research team worked to develop neural networks that closely approximate how humans and other biological systems learn to see. The group initially struggled with stabilizing simulated neural networks undergoing unsupervised

dictionary training, which involves classifying objects without having prior examples to compare them to.

"The issue of how to keep learning systems from becoming unstable really only arises when attempting to utilize biologically realistic, spiking neuromorphic processors or when trying to understand biology itself," said Los Alamos computer scientist and study coauthor Garrett Kenyon. "The vast majority of machine learning, deep learning, and AI researchers never encounter this issue because in the very artificial systems they study they have the luxury of performing global mathematical operations that have the effect of regulating the overall dynamical gain of the system."

The researchers characterize the decision to expose the networks to an artificial analog of sleep as nearly a last ditch effort to stabilize them. They experimented with various types of noise, roughly comparable to the static you might encounter between stations while tuning a radio. The best results came when they used waves of so-called Gaussian noise, which includes a wide range of frequencies and amplitudes. They hypothesize that the noise mimics the input received by biological neurons during slow-wave sleep. The results suggest that slow-wave sleep may act, in part, to ensure that cortical neurons maintain their stability and do not hallucinate.

The groups' next goal is to implement their algorithm on Intel's Loihi neuromorphic chip. They hope allowing Loihi to sleep from time to time will enable it to stably process information from a silicon retina camera in real time. If the findings confirm the need for sleep in artificial brains, we can probably expect the same to be true of androids and other intelligent machines that may come about in the future.

Watkins will be presenting the research at the Women in Computer Vision Workshop on June 14 in Seattle.

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Stroke bleeds in the brain not decreasing, Framingham study finds

Thinners could be factor, but in benefit-risk trade-off, are needed to prevent clots

San Antonio, Texas, USA - Brain bleeds called intracerebral hemorrhages remained stable in incidence among all age groups over the past 30 years, but they increased in people 75 and older, according to a new analysis of the Framingham Heart Study. The findings are in *JAMA Neurology*.

Use of anticoagulants also increased in senior adults threefold over the period, but authors cautioned against making too much of it.

"We are not advocating that people stop taking statins or anticoagulants," said report senior author Sudha Seshadri, MD, neurologist in the Long School of Medicine at The University of Texas Health Science Center at San Antonio. "Those therapies reduce the risk of ischemic strokes, which represent approximately nine of every 10 strokes, with intracerebral hemorrhages representing the other tenth."

Because of the increase in life expectancy and aging of the population, health care systems will likely see an increase in the number of patients with brain hemorrhages, said Dr. Seshadri, who is senior investigator of the Framingham Heart Study and at UT Health San Antonio directs the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases.

Imaging and medications

The report's lead author, Vasileios-Arsenios Lioutas, MD, a stroke neurologist at Beth Israel Deaconess Medical Center and Harvard Medical School, designed the study to assess trends in the incidence of intracerebral hemorrhages in 10,333 Framingham participants from 1948 to 2016. Of the participants, 129 experienced such a hemorrhage during study follow-up.

The years were divided into three periods: 1948-1986, 1987-1999 and 2000-2016.

"We wanted to account for changes in diagnostic approaches, and one of the main advancements was the CT scan, which started being used around 1980," Dr. Lioutas said. "Many things that could not previously be diagnosed as bleeds could be seen very easily after that time."

The late 1990s saw increased prescribing of blood thinners such as warfarin, which a series of trials showed to be effective at preventing clots arising from atrial fibrillation, a heart rhythm abnormality. In the 2000s, further preventative practices and additional medications were added.

"One of the possible explanations for why we saw more bleeds in older Framingham participants is that, by using these anticoagulant medications, we prevented adverse events that would potentially have killed them earlier in life," Dr. Lioutas said. "We prolonged their life expectancy and then, because we did, they were at risk to have a hemorrhage later in life."

"It's a bit of a balancing act," Dr. Seshadri said. "We want to be careful what message we send about this. Statins and anticoagulants have value in preventing life-altering or fatal events."

Hypertension's role

The study also examined risk factors for two types of brain hemorrhages. Lobar intracerebral hemorrhages occur closer to the surface of the brain, whereas deep intracerebral hemorrhages occur deeper within the brain matter and involve different structures.

Hypertension, previously thought to be more important as a risk factor in deep intracerebral hemorrhages, increased risk in both types, the study found.

Deep intracerebral hemorrhages are associated with changes in the very small vessels of the brain that are the consequence of longtime exposure to hypertension, Dr. Lioutas said.

Lobar hemorrhages also feature changes in small vessels, but the vessels are near the brain surface. Deposits of amyloid protein - best known for being linked to Alzheimer's disease - are believed to be a culprit in these hemorrhages.

"As was the case in previous research, we saw that these lines of distinction are not so clear," Dr. Lioutas said. "Especially in lobar hemorrhage, we saw that many people also had hypertension, so we now believe hypertension plays a role in both deep and lobar intracerebral hemorrhages."

The study shows that while clinical advances have been successful in decreasing stroke rates in developed countries, the decline is mostly for clot-related strokes and not in hemorrhagic strokes.

"We saw an increase in intracerebral hemorrhages in the older Framingham population, in a demographic group that is growing larger year by year in America and worldwide," Dr. Seshadri said. "We should find new means of prevention of these strokes, and at the same time health care systems should be ready to treat more hemorrhages in the future."

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Assessment of Incidence and Risk Factors of Intracerebral Hemorrhage Among Participants in the Framingham Heart Study Between 1948 and 2016

Vasileios-Arsenios Lioutas, MD; Alexa S. Beizer, PhD; Hugo J. Aparicio, MD; Jayandra J. Himali, PhD; Magdy H. Selim, MD; Jose Rafael Romero, MD; Sudha Seshadri, MD

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New study: Chemists at the University of Halle are able to induce uniform chirality

A way to spontaneously induce chirality in crystalline, liquid-crystalline and liquid substances

Chirality is a fundamental property of many organic molecules and means that chemical compounds can appear in not only one form, but in two mirror-image forms as well.

Chemists at Martin Luther University Halle-Wittenberg have now found a way to spontaneously induce chirality in crystalline, liquid-crystalline and liquid substances, without requiring any external influence.

The findings could be significant for the development of new active substances and for materials science.

The study was recently published in *Chemical Science* an international journal published by the Royal Society of Chemistry.

Chirality is found in almost all molecules occurring in nature.

"Molecules are spatial arrangements of interconnected atoms.

Many molecules, however, have not only one form, but at least two," explains Professor Carsten Tschierske, a chemist at MLU.

When these forms are mirror images of each other it is called chirality. Both mirror-image forms are produced in equal numbers during normal chemical reactions in the laboratory.

"However, things occur differently in nature: carbohydrates, amino acids and nucleic acids only have one dominant form," explains Tschierske.

And with good reason: for example, nucleic acids carry information about our DNA. Even the slightest changes to our genetic material can lead to serious diseases.

"If each nucleic acid had two forms, the structure of our DNA would be chaotic because there would be too many possible variations. Life as we know it would be impossible," states Tschierske.

The exact process that once created the uniform chirality in these molecules is still unknown.

Furthermore, it was long assumed that mixtures of mirror-image molecules can only separate spontaneously in crystalline materials.

However, in a study published in "Nature Chemistry" in 2014, Tschierske's team was able to show that this phenomenon of chiral cleavage can also be observed in liquids.

"This is significant because the origins of life are found in liquid aqueous systems," explains the chemist.

In this new study, his team went one step further.

The researchers found a way to not only generate chirality in liquids, but also to specifically transfer it to liquid-crystalline and crystalline materials without incurring any losses.

To do this, the scientists used benzil, a molecule that is normally achiral, in other words, has no mirror image, but can be twisted in such a way to make it chiral. "We already knew that benzil could crystallize in a uniform chiral shape," says Tschierske.

By modifying this molecule, the researchers were able to spontaneously generate molecules with uniform chirality even in a liquid state - and to maintain this state during conversions.

"These findings contribute to our understanding of the formation of uniform biochirality.

At the same time, our approach can also be used to synthesize chiral molecules and materials - without requiring expensive chiral precursors," explains Tschierske.

The study conducted in Halle contributes to our understanding of how uniform biochirality might have developed millions of years ago.

At the same time, it provides new insights into how chirality can be spontaneously generated.

There is a broad range of applications: for example, chiral substances can be used as active ingredients in medicine.

The research findings could also be used in a wide variety of materials, for example in optical information processing.

About the study: Reppe T. et al. Spontaneous mirror symmetry breaking in benzil-based soft crystalline, cubic liquid crystalline and isotropic liquid phases. Chemical Science (2020). doi: 10.1039/D0SC01396J https://doi.org/10.1039/D0SC01396J

https://bit.ly/3f9BOGn

Popular Heartburn Drug Famotidine May Help Fight Mild to Moderately Severe COVID-19 Cases

Oral famotidine is associated with improved outcomes in non-hospitalized patients with COVID-19

Famotidine is widely available over the counter at low cost, does not interact with other medications and has been safely used for suppression of gastric acid production over a wide range of oral doses from 20 mg once daily to 160 mg four times daily. According to a small case study published in the journal *Gut*, oral famotidine is associated with improved outcomes in non-hospitalized patients with COVID-19.

Management of patients with COVID-19, caused by the SARS-CoV-2 coronavirus, poses a major challenge to the biomedical community, governments and global population. Currently, most research focuses on vaccine development or pharmacological treatment strategies for hospitalized patients with COVID-19.

However, to reduce global morbidity and mortality, effective treatment strategies for non-hospitalized patients are required.

Famotidine, which belongs to a class of drugs known as histamine-2 receptor antagonists, may be a candidate medication for this.

"Our case series suggests, but does not establish, a benefit from famotidine treatment in outpatients with COVID-19," said Cold Spring Harbor Laboratory's Dr. Tobias Janowitz and colleagues.

The study involved 10 people (6 men; 4 women) who developed COVID-19 infection, all of whom happened to have been taking famotidine during their illness. Their ages ranged from 23 to 71 and they had a diverse range of ethnic backgrounds and known risk factors for COVID-19 severity, including high blood pressure and obesity.

The severity of five cardinal symptoms (cough, shortness of breath, fatigue, headache, and loss of taste/smell) as well as general unwellness as measured using a version of a 4-point scale normally applied to assess the severity of cancer symptoms (ECOG PS).

"The experience of a patient at one point in time is very valuable, but learning about the change in their experience over time is even more important," Dr. Janowitz said.

"Change indicates if the patients' condition is getting better or worse. A graded symptom score enables the physician and the patient to track symptoms using numbers."

"You may call up your doctor and say, I have headaches and shortness of breath, and am only able to do the basics for self-care, which would be grade 3 symptoms," he added.

"If you still had the symptoms two days later, but are now able to do light work, these symptoms would now be scored at grade 2."

"This approach makes it very easy for you and your doctor to document that your symptoms are improving. The value of this approach from a research perspective is that experiences from many patients become comparable and can be pooled for analysis."

Seven of the patients tested positive for COVID-19, using a swab test; two had antibodies to the infection; and one patient wasn't tested but was diagnosed with the infection by a doctor.

All started taking famotidine when they were feeling very poorly with COVID-19, the symptoms of which had been going on from 2 up to 26 days at that point.

The most frequently used dose was 80 mg taken three times a day, with the average treatment period lasting 11 days, but ranging from 5 to 21 days. All 10 patients said that symptoms quickly improved within 24-48 hours of starting famotidine and had mostly cleared up after 14 days.

Improvement was evident across all symptom categories assessed, but respiratory symptoms, such as cough and shortness of breath, improved more rapidly than systemic symptoms, such as fatigue.

Seven of the patients didn't experience any side effects while on famotidine, and in the three who did, these were mild, and all but temporary forgetfulness were known side effects associated with taking the drug.

"While promising, the findings might have been affected by 'the placebo effect,' and/or hazy recall, added to which the number of case study participants was small," the researchers said. "And it's not clear how famotidine might work: if it might incapacitate the virus in some way or alter a person's immune response to it."

"Clinically, we unreservedly share the opinion that well designed and informative studies of efficacy are required to evaluate candidate medications for COVID-19 as for other diseases."

Nevertheless, they suggest their findings warrant further more detailed study, adding that a clinical trial, testing the combination of famotidine with the antimalarial drug hydroxychloroquine in patients admitted to hospital with COVID-19, is already under way.

"An outpatient study of oral famotidine that investigates efficacy for symptom control, viral burden and disease outcome and assesses the effects of medication use on long term immunity should be considered to establish if famotidine may be of use in controlling COVID-19 in individual patients while also reducing the risk of SARS-CoV-2 transmission," the scientists said.

T. Janowitz et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. Gut, published online June 4, 2020; doi: 10.1136/gutjnl-2020-321852

This article is based on texts provided by Cold Spring Harbor Laboratory and BMJ.

https://bit.ly/2zlnMCp

Engineers put tens of thousands of artificial brain synapses on a single chip

The design could advance the development of small, portable AI devices

MIT engineers have designed a "brain-on-a-chip," smaller than a piece of confetti, that is made from tens of thousands of artificial brain synapses known as memristors -- silicon-based components that mimic the information-transmitting synapses in the human brain.

The researchers borrowed from principles of metallurgy to fabricate each memristor from alloys of silver and copper, along with silicon. When they ran the chip through several visual tasks, the chip was able to "remember" stored images and reproduce them many times over, in versions that were crisper and cleaner compared with existing memristor designs made with unalloyed elements.

Their results, published today in the journal *Nature Nanotechnology*, demonstrate a promising new memristor design for neuromorphic devices -- electronics that are based on a new type of circuit that processes information in a way that mimics the brain's neural architecture. Such brain-inspired circuits could be built into small, portable devices, and would carry out complex computational tasks that only today's supercomputers can handle.

"So far, artificial synapse networks exist as software. We're trying to build real neural network hardware for portable artificial intelligence systems," says Jeehwan Kim, associate professor of mechanical engineering at MIT. "Imagine connecting a neuromorphic device to a camera on your car, and having it recognize lights and objects and make a decision immediately, without having to connect to the internet. We hope to use energy-efficient memristors to do those tasks on-site, in real-time."

Wandering ions

Memristors, or memory transistors, are an essential element in neuromorphic computing. In a neuromorphic device, a memristor would serve as the transistor in a circuit, though its workings would more closely resemble a brain synapse -- the junction between two neurons. The synapse receives signals from one neuron, in the form of ions, and sends a corresponding signal to the next neuron.

A transistor in a conventional circuit transmits information by switching between one of only two values, 0 and 1, and doing so only when the signal it receives, in the form of an electric current, is of a particular strength. In contrast, a memristor would work along a gradient, much like a synapse in the brain. The signal it produces would vary depending on the strength of the signal that it receives. This would enable a single memristor to have many values, and therefore carry out a far wider range of operations than binary transistors.

Like a brain synapse, a memristor would also be able to "remember" the value associated with a given current strength, and produce the exact same signal the next time it receives a similar current. This could ensure that the answer to a complex equation, or the visual classification of an object, is reliable -- a feat that normally involves multiple transistors and capacitors.

Ultimately, scientists envision that memristors would require far less chip real estate than conventional transistors, enabling powerful, portable computing devices that do not rely on supercomputers, or even connections to the Internet.

Existing memristor designs, however, are limited in their performance. A single memristor is made of a positive and negative electrode, separated by a "switching medium," or space between the electrodes. When a voltage is applied to one electrode, ions from that electrode flow through the medium, forming a "conduction channel" to the other electrode. The received ions make up the electrical signal that the memristor transmits through the circuit. The size of the ion channel (and the signal that the memristor ultimately produces) should be proportional to the strength of the stimulating voltage.

Kim says that existing memristor designs work pretty well in cases where voltage stimulates a large conduction channel, or a heavy flow of ions from one electrode to the other. But these designs are less reliable when memristors need to generate subtler signals, via thinner conduction channels.

The thinner a conduction channel, and the lighter the flow of ions from one electrode to the other, the harder it is for individual ions to stay together. Instead, they tend to wander from the group, disbanding within the medium. As a result, it's difficult for the receiving electrode to reliably capture the same number of ions, and therefore transmit the same signal, when stimulated with a certain low range of current.

Borrowing from metallurgy

Kim and his colleagues found a way around this limitation by borrowing a technique from metallurgy, the science of melding metals into alloys and studying their combined properties.

"Traditionally, metallurgists try to add different atoms into a bulk matrix to strengthen materials, and we thought, why not tweak the atomic interactions in our memristor, and add some alloying element to control the movement of ions in our medium," Kim says.

Engineers typically use silver as the material for a memristor's positive electrode. Kim's team looked through the literature to find an element that they could combine with silver to effectively hold silver ions together, while allowing them to flow quickly through to the other electrode.

The team landed on copper as the ideal alloying element, as it is able to bind both with silver, and with silicon.

"It acts as a sort of bridge, and stabilizes the silver-silicon interface," Kim says.

To make memristors using their new alloy, the group first fabricated a negative electrode out of silicon, then made a positive electrode by depositing a slight amount of copper, followed by a layer of silver. They sandwiched the two electrodes around an amorphous silicon medium. In this way, they patterned a millimeter-square silicon chip with tens of thousands of memristors.

As a first test of the chip, they recreated a gray-scale image of the Captain America shield. They equated each pixel in the image to a corresponding memristor in the chip. They then modulated the conductance of each memristor that was relative in strength to the color in the corresponding pixel.

The chip produced the same crisp image of the shield, and was able to "remember" the image and reproduce it many times, compared with chips made of other materials.

The team also ran the chip through an image processing task, programming the memristors to alter an image, in this case of MIT's Killian Court, in several specific ways, including sharpening and blurring the original image. Again, their design produced the reprogrammed images more reliably than existing memristor designs.

"We're using artificial synapses to do real inference tests," Kim says. "We would like to develop this technology further to have larger-scale arrays to do image recognition tasks. And some day, you might be able to carry around artificial brains to do these kinds of tasks, without connecting to supercomputers, the internet, or the cloud."

This research was funded, in part, by the MIT Research Support Committee funds, the MIT-IBM Watson AI Lab, Samsung Global Research Laboratory, and the National Science Foundation.

https://bit.ly/37hxDFO

Kawasaki-like syndrome linked to COVID-19 in children is a new condition

A study on children suffering from severe inflammatory symptoms shows the condition is new and distinct from Kawasaki disease.

In April, researchers in the UK and several European countries with high numbers of COVID-19 cases recognised a new inflammatory syndrome in children that was similar to Kawasaki disease, a rare syndrome known to affect young children.

Now in a paper published today in the *Journal of the American Medical Association* researchers have identified the main symptoms and clinical markers of the new syndrome. This will help clinicians diagnose and treat the condition and researchers to understand it further and find new treatments.

The study, led by Imperial College Academic Health Science Centre (AHSC) researchers, involved clinicians and academic partners in hospitals across England, including Great Ormond Street Hospital (GOSH) and the Evelina London Children's Hospital, as well the Kawasaki Disease Research Center at the University of California San Diego.

The condition, which the researchers have named Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS), was studied in 58 children admitted to eight hospitals in England.

The condition is believed to be extremely rare, but there are concerns about long-lasting coronary damage. Less than 200 cases have been reported in England with a range of symptoms and severity and most children have already recovered.

Lead author Dr Elizabeth Whittaker, from the Department of Infectious Disease at Imperial College London and a consultant in paediatric infectious diseases and immunology at Imperial College Healthcare NHS Trust, said: "The new condition, PIMS-TS, is extremely rare but it can make a child very ill, so it's important to characterise the disease properly so we can provide close monitoring and the best treatment.

"For any parents worried about their children, I would urge them to follow their usual instincts - whatever would normally prompt you to visit your GP or A&E with your child still applies here."

Dr Julia Kenny, consultant in paediatric infectious diseases and immunology at Evelina London, said: "Our analysis has shown that this is indeed a new condition. Untreated, there is a risk of severe complications in very unwell children, but with early identification and treatment the outcome is excellent, with the children we are reviewing after discharge completely well.

"For clinicians, it's important that we build collaborative research to quickly improve our understanding of the condition and provide the best evidence-based treatment for our patients."

PIMS-TS appears to be more likely to affect older children than Kawasaki disease (average nine years old versus four years old respectively) and presents more often with abdominal pains and diarrhoea alongside the common features such as persistent fever. It also appears to affect a higher proportion of Black and Asian patients.

Blood tests also show different results, with PIMS-TS patients showing more markers of inflammation and cardiac enzymes, which suggest the heart is under strain.

Kawasaki disease is known to damage the coronary artery in such a way that as the child grows the artery does not, leading to a reduction in the amount of blood that can reach the heart. Immune therapy is known to help alleviate these problems, so has been used on patients with PIMS-TS as well, although the team say differences in the two diseases mean this needs to be investigated further and treatment should be carefully monitored.

Lead researcher Professor Michael Levin, from the Department of Infectious Disease at Imperial College London, said: "The new disease presents in a number of ways and can have serious complications. However, the more we learn the better prepared we are to intervene and prevent worse outcomes. For example, patients who develop shock and cardiac failure have a different pattern of blood tests that may help to identify the at-risk group for targeted treatment."

While the team cannot say for certain that PIMS-TS is caused by COVID-19, 45 of the 58 children had evidence of current or past COVID-19 infection, and the researchers say the emergence of a new inflammatory condition during a pandemic is unlikely to be a coincidence.

The majority of children with indications of infection had antibodies for the new coronavirus, suggesting PIMS-TS happens after infection, potentially as a result of an immune system overreaction.

For this reason, the researchers also say understanding more about PIMS-TS could help a more general understanding of COVID-19 and its effects, even in adults. Because PIMS-TS is so distinct, it is easy to study individuals with high inflammation, which may be harder to identify in the general population.

The researchers are collaborating with teams across Europe and the USA that are also studying the new condition in the hopes of rapidly learning more about PIMS-TS and COVID-19. For example, if the condition is caused by an immune system overreaction, this could have implications for the use of vaccines.

Dr Alasdair Bamford, consultant and specialty lead in paediatric infectious diseases at Great Ormond Street Hospital, said: "An important next step will be to review this data in the context of other studies being published from around the world. This will help inform management guidelines and to further refine the case definition. Recruitment of children into observational studies and clinical trials will be key to creating an evidence base for the best treatment."

This research is an example of the work carried out by Imperial College Academic Health Science Centre, a joint initiative between Imperial College London and three NHS hospital trusts. It aims to

transform healthcare by turning scientific discoveries into medical advances to benefit local, national and global populations in as fast a timeframe as possible.

https://bit.ly/3fneW6D

Nobel laureate Tasuku Honjo to sue Japanese drug firm for 22 billion yen

Which he believes he should get for supporting the drug firm in a patent dispute.

By Dennis Normile

In another high-profile case of a Japanese scientist fighting for a share of the profits generated by a key discovery, Nobel laureate Tasuku Honjo last Friday announced he plans to sue Osaka, Japan–based Ono Pharmaceutical for 22 billion yen ($200 million) he believes he should get for supporting the drug firm in a patent dispute.

Immunologist Tasuku Honjo celebrates his receipt of the Nobel Prize in 2018 with his wife, Shigeko Honjo. **Kyodo via AP Images**

The 78-year-old Kyoto University immunologist shared the 2018 Nobel Prize in Physiology or Medicine with James Allison, of the MD Anderson Cancer Center at the University of Texas, "for their discovery of cancer therapy by inhibition of negative immune regulation." Both discovered ways to remove brakes on the immune system that prevent it from attacking tumor cells, although they identified different mechanisms. Honjo's discovery focused on a molecule expressed in dying T cells, which he called programmed death 1, or PD-1. Later, he and others found the molecule could be harnessed for cancer therapies.

In the years since the discovery, competing groups have developed PD-1–related drugs for treating cancer. Ono co-owns key patents with Honjo. The Japanese company worked together with Bristol Myers Squibb to develop Opdivo, which was approved in both Japan and the United States to treat metastatic melanoma in 2014. That same year, Merck won approval for Keytruda, an anticancer drug that also targets PD-1 receptors.

Ono and Bristol Myers Squibb sued Merck for patent infringement. Honjo traveled to the United States to appear as an expert witness in court and provided other support for the suit. In 2017, Merck agreed to pay $625 million in patent royalties, as well as a portion of Keytruda's sales revenue between 2017 and 2026, to Ono and its partners.

Honjo says his efforts related to the case were not anticipated in his original compensation agreement with Ono, so he says the company promised him 40% of any settlement. Honjo says he has not received his share of the payment. After 3 years of fruitless negotiations with the company, he has decided to take the matter to court.

An Ono public relations official says the company has no comment.

The stage for this dispute was set in the early 2000s when Honjo wanted to patent his PD-1 discovery for use in treating cancer. At the time, Japanese universities, including Kyoto, "didn't have any management capacity or the knowledge to apply for patents; they didn't even have money to support applications," he says. So he turned to Ono. "They did not do anything scientifically, [but] they helped me to apply for a patent," Honjo says.

Since then, Japan's universities have gotten more sophisticated in handling intellectual property, though their experience doesn't match that accumulated by U.S. universities, he says. And corporations in Japan are still taking advantage of the situation, he asserts. "We believe this lawsuit is not only for my own case, but also to support many other scientists in academia," Honjo says. He has pledged to donate his share of any settlement to Kyoto University for a fund to support young investigators.

This is not the first time a Japanese Nobel laureate has become embroiled in litigation over compensation for their prize-winning work.

In the early 2000s, materials scientist Shuji Nakamura took his former employer, Nichia Corporation, to court claiming he had not been properly compensated for developing a blue light-emitting diode (LED). At the time, Japan's patent laws allowed employees named as inventors to cede rights to their employers for reasonable compensation without providing any guidance to the meaning of reasonable.

In 2004, a Japanese court noted that Nichia had earned more than $1.1 billion in profits from the blue LED and awarded Nakamura a stunning $180 million. Nichia appealed and in 2005 Nakamura accepted a $9 million payment to settle the matter. By that time, he had moved to the University of California, Santa Barbara. He shared the 2014 Nobel Prize for Physics "for the invention of efficient blue light-emitting diodes" with two other Japanese scientists.

"Nakamura's challenge resulted in a great improvement [to the status] of scientists employed by companies, but that didn't affect the balance between industry and academia," Honjo says.

Although Honjo and Ono are now opponents in the new case, they are allied with Bristol Myers Squibb in yet another ongoing battle over patents related to PD-1. In May 2019, a U.S. court ruled that six U.S. patents covering PD-1 based cancer treatments originally granted to Honjo and Ono should be revised to include two researchers, Gordon Freeman and Clive Wood, at the Dana-Farber Cancer Institute.

The court found the three scientists collaborated extensively and are joint inventors of the six patents. Honjo and his partners have appealed the ruling.

https://bit.ly/30xMnPy

New books present the PhyloCode, an evolution-based system for naming organisms

Move over, Linnaeus: There's a new way of naming organisms.

by Natalie Van Hoose

Scientists have formalized an alternative set of rules 285 years after the publication of the first edition of "Systema Naturae," the landmark volume marking the beginning of the rank-based system for categorizing and naming life. Known as the PhyloCode, this system defines scientific names based on evolutionary relationships. Two new books, "International Code of Phylogenetic Nomenclature (PhyloCode)" and "Phylonyms: A Companion to the PhyloCode," outline the rules of the PhyloCode and apply them to some of nature's major clades—groups of organisms consisting of an ancestor and all its descendants.

"This is truly the most significant contribution to the scientific naming system since Linnaeus," said Nico Cellinese, treasurer of the International Society for Phylogenetic Nomenclature, which oversaw the publication of the books and ratified the rules.

Cellinese, associate curator of bioinformatics at the Florida Museum of Natural History and the University of Florida Herbarium, heralded the PhyloCode as "a nomenclature system for the modern age. This provides us with a tool to communicate tree-based concepts," she said, referring to phylogenetics, the study of the evolutionary relationships between organisms.

The product of more than 20 years' labor, "PhyloCode" is the work of Kevin de Queiroz, research zoologist at the Smithsonian's National Museum of Natural History, and Philip Cantino, professor emeritus of environmental and plant biology at Ohio University. De Queiroz, Cantino and Jacques Gauthier of Yale University also edited the accompanying volume "Phylonyms," in which nearly 200

experts established PhyloCode-governed names and phylogenetic definitions for many clades of organisms.

De Queiroz said when he and Gauthier first discovered the underlying theoretical principle of the PhyloCode in the mid-1980s, their intent was not to create a new scientific naming system.

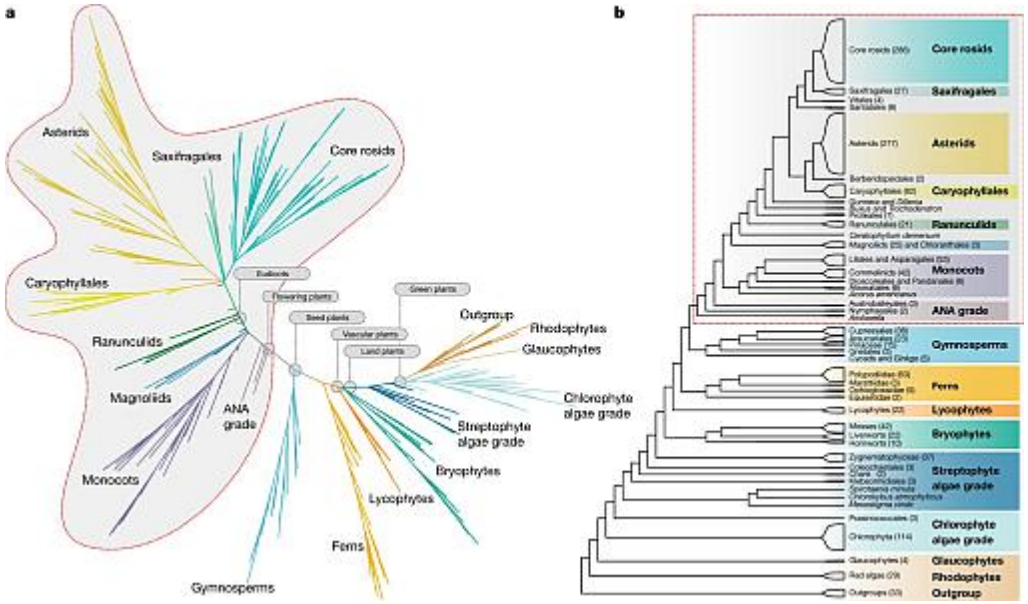
"We just kind of stumbled on this idea," he said. "We were trying to decide where to place certain names on a phylogenetic tree. In the process of talking about it, we realized there could be a different way of defining names—by describing evolutionary relationships. Since definitions are the foundation of any naming system, this opened up the possibility for a new system: the PhyloCode."

Linnaeus' system predated the concept of evolution by more than 100 years and therefore lacked the ability to incorporate newfound knowledge about ancestral relationships between organisms, said Pamela Soltis, curator of the Florida Museum's Molecular Lab, distinguished professor at UF and president of the International Society for Phylogenetic Nomenclature.

"Linnaeus was revolutionary. But it's important to remember that he established these ranks more than a century before we knew about evolution," she said. "So, why do we keep trying to put what we know about evolution in a system that wasn't built to reflect it?"

While the tradition of ranking life forms dates back to Plato and Aristotle, Linnaeus refined that tradition, creating a formal hierarchy of categories—such as kingdoms, classes, orders and species—that nested within one another. But these ranks are ultimately human constructs and often rely on subjective criteria, which can lead to confusion and instability. When a name changes based on new findings, it can have a cascading effect, de Queiroz said.

Take termites, which until about a decade ago, made up the order Isoptera. Subsequent studies showed they're actually a subgroup of roaches, which had their own order, Blattodea. This resulted in the "demotion" of termites to the rank of family and a cascade of headache-inducing name changes down through its subgroups—even though termites, as a clade of organisms with a common ancestor, did not change.



A phylogeny is a map of the evolutionary relationships between organisms. This tree represents the relationships between green plants. **Leebens-Mack et al. In Nature**

"With the PhyloCode, that doesn't happen. You can use ranks, but they have no role in the naming," Cantino said. "We're retaining most existing names, but tying them to clades so that they won't change if they change in rank. Once we made the decision that the PhyloCode would govern only clade names, not species names, which are still governed by the traditional codes, we did whatever we could to make the two systems compatible."

Another benefit of the PhyloCode is increased clarity, said Cellinese, who spearheaded the development of RegNum, the online registration database for names created using the rules of the PhyloCode, including those in "Phylonyms."

"Clades have very well-defined points of references—the tree, ancestors, nodes, branches," she said. "Otherwise, you have to rely on ranks, which don't exist in nature, or groups defined by traits, physical characteristics that can be ambiguous. What looks red to you may look pink to me."

This subjectivity also makes groups defined by traits difficult to compute with algorithms, she said.

De Queiroz likened it to searching for a house using subjective directions such as "Turn right at the tall tree." The PhyloCode offers a definition that is akin to GPS coordinates, making it easier to use computer programs to navigate evolutionary trees.

The PhyloCode is not without its opponents, and much of de Queiroz and Cantino's time has been spent responding to critiques. But the authors said they hope the younger generation of scientists, who have been brought up on "tree thinking," will embrace the system and step into leadership roles to further develop it in the future.

What might Linnaeus have said about this new system? Soltis was optimistic. "I think if he knew what we know now, he would say, 'Do it.'" The books are now available for preorder from CRC Press, part of the Taylor and Francis Group, and will publish June 9.

Cellinese, Soltis and the Florida Museum's Douglas Soltis and Walter Judd contributed names to the "Phylonyms" volume.

https://bit.ly/30Bok24

Kidneys deteriorate with age, regardless of health

Kidney function deteriorates with age, even if we do not have any other diseases

An international study that has been carried out on nearly 3000 people in Norway, Germany, and Iceland, shows that our kidney function deteriorates with age, even if we do not have any other diseases. The results from the study have recently been published in the reputable journal for kidney diseases, *Journal of the American Society of Nephrology (JASN).* In the study, the researchers have examined the kidney function of a group of people between the ages of 50 and 70, and two groups of people between the ages of 70 to 95, to discover how the kidney function develops.

- What we see is that what happens in our kidneys when we age is representative of all the other things that happen in our bodies. The kidney function deteriorates, not because we get ill, but as part of ageing, Bjørn Odvar Eriksen explains, who is a Professor at the Department of Clinical Medicine at UiT and leader of the Metabolic and Renal Research Group.

Eriksen is the lead author of the article that has been published in *JASN*.

- Loss of kidney function is something that happens to all humans and is thus a way to determine ageing in general. There is still variation as to how quickly this happens, and we still do not have good answers as to why this variation occurs. We have examined many factors that can play a part as to why some of us experience larger loss of kidney function than others, he adds.

One of the groups that have participated in the study consists of over 1600 people and stems from The Tromsø Study, which is Norway's most comprehensive and best participated population study throughout 40 years. This group has been through the different examinations three times; between 2007 to 2009, 2013 to 2015, and 2018 to 2020. The last iteration of the study is still ongoing at The University Hospital of North Norway (UNN) and is lead by Associate Professor Toralf Melsom.

- No other study has done these kinds of examinations on a part of the normal population. That is why this study is so unique, Eriksen says.

The researchers use a precise method of measuring kidney function. They inject a substance into the blood veins that only separates into the kidneys, and let a few hours pass before they measure how

much of the substance remains in the blood. This gives a measure of the kidney's ability to remove toxins and waste products. Eriksen explains that more people may experience loss of kidney function as it becomes more common to survive diseases like cancer and heart and vascular diseases.

- For those who experience loss of kidney function at a high age, this is a considerable burden. That is why this is an area that needs further research to find more answers. We are still looking for the fountain of youth, Eriksen says.

https://bit.ly/3cUrErL

Fabric Masks Need 3 Specific Layers to Effectively Block Coronavirus, WHO Says

Inner layer that absorbs, middle layer that acts as a filter, and outer layer made from a non-absorbent material

Anna Medaris Miller, Business Insider

Fabric masks, either homemade or store-bought, can help prevent the spread of the novel coronavirus in settings where physical distancing is difficult, according to new research that informed the World Health Organisation's updated guidelines on mask wearing.

The guidelines, set to be released today, detail the type of fabric masks that are effective. They should have three layers: an inner layer that absorbs, a middle layer that acts as a filter, and an outer layer made from a non-absorbent material like polyester.

Those layers in that order can "provide a mechanistic barrier," epidemiologist Maria D. Van Kerkhove, the WHO technical lead on COVID-19, said during a media briefing from Geneva Friday. The guidance, she emphasised, is based on "new, novel research" commissioned by the WHO.

Fabric masks should also be cleaned and worn correctly, since contaminated hands can infect a person adjusting their mask or frequently taking it on or off, Tedros Adhanom Ghebreyesus, the WHO director-general said.

The specifics of how to wear and clean them will be included in the soon-to-be-released guidance.

The updated guidelines also encourage people working in clinical settings in areas with widespread coronavirus transmission to wear medical masks – even if they're not working directly with COVID-19 patients.

"That means for example, that when a doctor is doing a walk around on the cardiology or palliative care units, where there are no confirmed COVID-19 patients, they should still wear a medical mask," Tedros said.

They also say that, in areas with community transmission and in settings where physical distancing is difficult, like on public transportation or in a grocery store, governments should encourage community members to wear masks.

Those over 60 and with underlying conditions should wear medical masks in such situations, the director-general said.

The WHO stressed that masks alone cannot defeat the virus

What hasn't changed in the WHO mask-wearing guidelines is advice that people who are sick with COVID-19 remain home, consult with their healthcare providers, and seek care if necessary, isolate themselves, and have their contacts quarantined.

"If it's absolutely necessary for a sick person or a contact to leave the house, they should wear a medical mask," Tedros said.

The WHO still recommends that caretakers of COVID-positive people should wear a medical mask while in the same room as the infected person, and that healthcare workers wear medical masks and other PPE when working with suspected or confirmed COVID-19 patients.

And the organisation continues to emphasise that masks alone cannot defeat the coronavirus, and can lead to a false sense of security leading people to slack on other important prevention measures.

"I cannot say this clearly enough: Masks alone will not protect you from COVID-19. Masks are not a replacement for physical distancing, hand hygiene, and other public health measures," Tedros said.

"Masks are only of benefit as part of a comprehensive approach in the fight against COVID-19," he continued. "The cornerstone of the response in every country must be to find, isolate, test, and care for every case, and to trace and quarantine every contact. That's what we know works."

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Deadly superbug could get a vigorous foe in repurposed antibiotic

Unmasked with new type of "nutrient-limited" media that better mimics conditions inside the body

USC researchers have discovered that an old antibiotic may be a powerful new tool against a deadly superbug, thanks to an innovative screening method that better mimics conditions inside the human body.

The antibiotic, rifabutin, is "highly active" in fighting multidrug-resistant Acinetobacter baumannii, a significant cause of life-threatening infections in medical facilities, researchers found.

The study appears today in *Nature Microbiology*.

"Rifabutin has been around for more than 35 years, and no one has ever studied it for Acinetobacter infections before," said first author Brian Luna, assistant professor of molecular microbiology and immunology at Keck School of Medicine of USC. "Going forward, we may find many new antibiotics that have been missed over the last 80 years because the screening tests used to discover them were suboptimal."

Rifabutin is used to treat TB, especially in people with HIV/AIDS who can't tolerate a similar drug, rifampin. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.

Until now, it hadn't been tried against Acinetobacter baumannii, which emerged during the Iraq War as a troop-killing superbug in military treatment facilities. Acinetobacter causes pneumonia, meningitis and bloodstream infections; it tends to strike patients requiring lengthy hospital stays and invasive devices like catheters and ventilators.

Each year, Acinetobacter baumannii is responsible for about 2% of the 99,000 U.S. deaths from hospital-acquired infections, according to the Centers for Disease Control and Prevention.

One reason rifabutin's superpower against superbugs was overlooked is because of current screening techniques, researchers said. Since the 1940s, new or existing antibiotics have been tested against bacteria grown in "rich culture media," a nutrient-packed broth or gel which speeds up the process by making the bacteria to grow rapidly.

"But bacteria grow very differently inside the human body," said Brad Spellberg, chief medical officer at the Los Angeles County-University of Southern California Medical Center and senior author of the study. So, the team designed a new type of "nutrient-limited" media that better mimics conditions inside the body. They hypothesized that the more realistic media might unmask antibiotics with hidden strengths.

They found that rifabutin was vigorously active against Acinetobacter baumannii grown in the nutrient-limited media (as well as in animal tissue) but not effective against bacteria grown in the more commonly used media.

The scientists discovered that rifabutin uses a unique, Trojan-horse strategy to trick the bacteria into actively importing the drug inside itself, bypassing the bacterial outer cell defenses. This "pump" that imports the drug is only active in the more human-like media. In

traditional rich culture media, high levels of iron and amino acids suppress the pump's activity, researchers found.

"Rifabutin can be used immediately to treat such infections because it is already FDA-approved, cheap and generic, and on the market," Spellberg said. "But we would like to see randomized controlled human trials to prove its efficacy, so we know for sure one way or the other."

More information: *B. Luna et al, A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant Acinetobacter baumannii, Nature Microbiology (2020).* *DOI: 10.1038/s41564-020-0737-6*

https://bit.ly/2C1yFKD

Sun-Like Star Kepler-160 Has Super-Earth in Habitable Zone

Astronomers using data from NASA's Kepler space telescope have discovered two new planets in the Kepler-160 planetary system.

by Natali Anderson

One of the new planets is the super-Earth-sized transiting world in the host star's habitable zone. Kepler-160 is a Sun-like star located 3,141 light-years away in the constellation of Lyra.

Also known as KOI-456 and KIC 7269974, the star is 1.12 times bigger than our Sun and is just 1% more luminous.

In 2010, astronomers detected two massive transiting planets, Kepler-160b and c, in very close orbits around the star.

Kepler-160b has a radius of 1.7 times that of the Earth and is in a 4.3-day orbit, while Kepler-160c, with a radius of about 3.1 Earth radii, orbits the star with a period of 13.7 days.

"Their surface temperatures would certainly make them hotter than a baking oven and everything but hospitable for life as we know it," said Max Planck Institute for Solar System Research astronomer René Heller and colleagues.

"But tiny variations in the orbital period of planet Kepler-160c gave scientists a signature of a third planet that had yet to be confirmed."

In the new study, Dr. Heller and co-authors analyzed archival data from the Kepler space telescope.

"Our analysis suggests that Kepler-160 is orbited not by two but by a total of four planets," Dr. Heller said. "One of the two planets that we found is Kepler-160d, the previously suspected planet responsible for the distorted orbit of Kepler-160c."

Kepler-160d is a non-transiting planet with a mass higher than Earth's and an orbital period between about 5 and 50 days.

The fourth planet in the system, Kepler-160e (also designated KOI-456.04), is probably a transiting planet with a radius of 1.9 times that of the Earth and an orbital period of 378 days.

"Given its Sun-like host star, the very Earth-like orbital period results in a very Earth-like insolation from the star — both in terms of the amount of the light received and in terms of the light color," Dr. Heller said.

"All things considered, Kepler-160e sits in a region of the habitable zone that is comparable to the Earth's position around the Sun."

"Kepler-160e is relatively large compared to many other planets that are considered potentially habitable," he said.

"But it's the combination of this less-than-double the size of the Earth planet and its solar type host star that make it so special and familiar."

"If Kepler-160e has a mostly inert atmosphere with a mild Earth-like greenhouse effect, then its surface temperature would be 5 degrees Celsius on average, which is about 10 degrees lower than the Earth's mean global temperature."

The discovery is described in paper published in the journal *Astronomy & Astrophysics*.

René Heller et al. 2020. Transit least-squares survey III. A 1.9 R⊕ transit candidate in the habitable zone of Kepler-160 and a nontransiting planet characterized by transit-timing variations. A&A 638, A10; doi: 10.1051/0004-6361/201936929

https://bit.ly/2MTfyVi

COVID-19 false negative results if used too early

Test that relies on viral genetic material gives false negative if used too early on those infected.

In a new study, Johns Hopkins researchers found that testing people for SARS-CoV-2 -- the virus that causes COVID-19 -- too early in the course of infection is likely to result in a false negative test, even though they may eventually test positive for the virus.

A report on the findings was published in the May 13 issue of *Annals of Internal Medicine*.

"A negative test, whether or not a person has symptoms, doesn't guarantee that they aren't infected by the virus," says Lauren Kucirka, M.D., Ph.D., M.Sc., obstetrics and gynecology resident at Johns Hopkins Medicine. "How we respond to, and interpret, a negative test is very important because we place others at risk when we assume the test is perfect. However, those infected with the virus are still able to potentially spread the virus."

Kucirka says patients who have a high-risk exposure should be treated as if they are infected, particularly if they have symptoms consistent with COVID-19. This means communicating with patients about the tests' shortcomings. One of several ways to assess for the presence of SARS-CoV-2 infection is a method called reverse transcriptase polymerase chain reaction (RT-PCR). These tests rapidly make copies of and detect the virus's genetic material. However, as shown in tests for other viruses such as influenza, if a swab misses collecting cells infected with the virus, or if virus levels are very low early during the infection, some RT-PCR tests can produce negative results. Since the tests return relatively rapid results, they have been widely used among high-risk populations such as nursing home residents, hospitalized patients and health care workers. Previous studies have shown or suggested false negatives in these populations.

For the new analysis, Johns Hopkins Medicine researchers reviewed RT-PCR test data from seven prior studies, including two preprints and five peer-reviewed articles. The studies covered a combined total of 1,330 respiratory swab samples from a variety of subjects including hospitalized patients and those identified via contact tracing in an outpatient setting.

Using RT-PCR test results, along with reported time of exposure to the virus or time of onset of measurable symptoms such as fever, cough and breathing problems, the researchers calculated the probability that someone infected with SARS-CoV-2 would have a negative test result when they had the virus infection. In the published studies, health care providers collected nasal and throat samples -from patients and noted the time of virus exposure or symptom -onset and sample collection. From this data, the Johns Hopkins researchers calculated daily false-negative rates, and have made their statistical code and data publicly available so results can be updated as more data are published.

The researchers estimated that those tested with SARS-CoV-2 in the four days after infection were 67% more likely to test negative, even if they had the virus. When the average patient began displaying symptoms of the virus, the false-negative rate was 38%. The test performed best eight days after infection (on average, three days after symptom onset), but even then had a false negative rate of 20%, meaning one in five people who had the virus had a negative test result.

"We are using these tests to rule out COVID-19, and basing decisions about what steps we take to prevent onward transmission, such as selection of personal protective equipment for health care workers," says Kucirka. "As we develop strategies to reopen services, businesses and other venues that rely on testing and contact tracing, it is important to understand the limitations of these tests."

Ongoing efforts to improve tests and better understand their performance in a variety of contexts will be critical as more people are infected with the virus and more testing is required. The sooner people can be accurately tested and isolated from others, the better we can control the spread of the virus, the researchers say.

Additional authors include Denali Boon, Stephen Lauer, Oliver Layendecker and Justin Lessler and of Johns Hopkins.

Funding for the study was provided by the National Institute of Allergy and Infectious Diseases (R01AI135115 and T32DA007292), the Johns Hopkins Health System and the U.S. Centers for Disease Control and Prevention (NU2GGH002000).

The authors had no conflict of interest to report.

https://bit.ly/2XSkj7E

HKUST scientists develop world's first spherical artificial eye with 3D retina

World's first 3D artificial eye with capabilities better than existing bionic eyes, some cases even exceeding those of the human eyes

An international team led by scientists at the Hong Kong University of Science and Technology (HKUST) has recently developed the world's first 3D artificial eye with capabilities better than existing bionic eyes and in some cases, even exceed those of the human eyes, bringing vision to humanoid robots and new hope to patients with visual impairment.

Scientists have spent decades trying to replicate the structure and clarity of a biological eye, but vision provided by existing prosthetic eyes - largely in the form of spectacles attached with external cables, are still in poor resolution with 2D flat image sensors. The Electrochemical Eye (EC-Eye) developed at HKUST, however, not only replicates the structure of a natural eye for the first time, but may actually offer sharper vision than a human eye in the future, with extra functions such as the ability to detect infrared radiation in darkness.

The key feature allowing such breakthroughs is a 3D artificial retina - made of an array of nanowire light sensors which mimic the photoreceptors in human retinas. Developed by Prof. FAN Zhiyong and Dr. GU Leilei from the Department of Electronic and Computer Engineering at HKUST, the team connected the nanowire light sensors to a bundle of liquid-metal wires serving as nerves behind the man-made hemispherical retina during the experiment, and successfully replicated the visual signal transmission to reflect what the eye sees onto the computer screen.

In the future, those nanowire light sensors could be directly connected to the nerves of the visually impaired patients. Unlike in a human eye where bundles of optic nerve fibers (for signal transmission) need to route through the retina via a pore - from the front side of the retina to the backside (thus creating a blind spot in human vision) before reaching the brain; the light sensors that now scatters across the entire man-made retina could each feed signals through its own liquid-metal wire at the back, thereby eliminating the blind spot issue as they do not have to route through a single spot.

Apart from that, as nanowires have even higher density than photoreceptors in human retina, the artificial retina can thus receive more light signals and potentially attain a higher image resolution than human retina - if the back contacts to individual nanowires are made in the future. With different materials used to boost the sensors' sensitivity and spectral range, the artificial eye may also achieve other functions such as night vision.

"I have always been a big fan of science fiction, and I believe many technologies featured in stories such as those of intergalactic travel, will one day become reality. However, regardless of image resolution, angle of views or user-friendliness, the current bionic eyes are still of no match to their natural human counterpart. A new technology to address these problems is in urgent need, and it gives me a strong motivation to start this unconventional project," said

Prof. Fan, whose team has spent nine years to complete the current study from idea inception.

The team collaborated with the University of California, Berkeley on this project and their findings were recently published in the prestigious scientific journal *Nature*.

"In the next step, we plan to further improve the performance, stability and biocompatibility of our device. For prosthesis application, we look forward to collaborating with medical research experts who have the relevant expertise on optometry and ocular prosthesis," Prof. Fan added.

The working principle of the artificial eye involves an electrochemical process which is adopted from a type of solar cell. In principle, each photo sensor on the artificial retina can serve as a nanoscale solar cell. With further modification, the EC-Eye can be a self-powered image sensor, so there is no need for external power source nor circuitry when used for ocular prosthesis, which will be much more user-friendly as compared with the current technology.

https://bit.ly/37nCiWN

Human eggs prefer some men's sperm over others, research shows

Different women's eggs attract different men's sperm—and not necessarily their partner's.

Human eggs use chemical signals to attract sperm. New research from Stockholm University and Manchester University NHS Foundation Trust shows that eggs use these chemical signals to choose sperm. Different women's eggs attract different men's sperm—and not necessarily their partner's.

Humans spend a lot of time and energy choosing their partner. A new study by researchers from Stockholm University and Manchester University NHS Foundation Trust (MFT) shows that choosing your partner continues even after sex—human eggs can "choose" sperm.

"Human eggs release chemicals called chemoattractants that attract sperm to unfertilized eggs. We wanted to know if eggs use these chemical signals to pick which sperm they attract," said John Fitzpatrick, an Associate Professor at Stockholm University.

The researchers examined how sperm respond to follicular fluid, which surrounds eggs and contains sperm chemoattractants. The researchers wanted to find out if follicular fluids from different females attracted sperm from some males more than others.

Dr John Fitzpatrick, Wallenberg Academy Fellow, Department of Zoology, Stockholm University. Credit: Magnus Bergström/Knut and Alice Wallenberg Foundation

Microscopic mate choice

"Follicular fluid from one female was better at attracting sperm from one male, while follicular fluid from another female was better at attracting sperm from a different male," said Professor Fitzpatrick. "This shows that interactions between human eggs and sperm depend on the specific identity of the women and men involved."

The egg does not always agree with the women's choice of partner. The researchers found that eggs did not always attract more sperm from their partner compared to sperm from another male.

Is this egg or sperm choice? Professor Fitzpatrick explained that sperm have only one job—to fertilize eggs—so it doesn't make sense for them to be choosy. Eggs on the other hand can benefit by picking high quality or genetically compatible sperm.

"The idea that eggs are choosing sperm is really novel in human fertility," said Professor Daniel Brison, the scientific director of the Department of Reproductive Medicine at Saint Marys' Hospital, which is part of MFT, and the senior author of this study.

The University of Manchester Honorary Professor added: "Research on the way eggs and sperm interact will advance fertility

treatments and may eventually help us understand some of the currently 'unexplained' causes of infertility in couples."

"I'd like to thank every person who took part in this study and contributed to these findings, which may benefit couples struggling with infertility in future."

The article "Chemical signals from eggs facilitate cryptic female choice in humans" is published in the scientific journal *Proceedings of the Royal Society B*.

More information: *Chemical signals from eggs facilitates cryptic female choice in humans, Proceedings of the Royal Society B, rspb.royalsocietypublishing.or ... .1098/rspb.2020.0805*

https://bit.ly/2XXIUYL

Sounds of sickness: Perceptions of coughs, sneezes not diagnosed accurately

You're standing in the store's check-out line, and the customer behind you viciously coughs. Is that person sick or simply have a throat tickle?

Nicholas Michalak

Chances are you're misidentifying the origins of those sounds, according to a newly published University of Michigan study in the Proceedings of the Royal Society B: Biological Sciences.

The more disgusting people perceive a sound to be, the more likely they were to judge that it came from an infected person, regardless of whether it did.

"We find no evidence that perceivers can reliably detect pathogen threats from cough and sneeze sounds, even though they are reasonably certain they can," said Nicholas Michalak, the study's lead author and a U-M psychology graduate student.

Unlike other research indicating perceivers can accurately diagnose infection using other senses, such as sight and smell, researchers at U-M and University of California-Irvine found that people over perceive pathogen threats in subjectively disgusting sounds.

Participants in four studies judged whether cough and sneeze sounds were produced by people infected with a communicable disease or not. Researchers found no evidence that these participants could accurately identify the origins through auditory cues. On average, they guessed approximately four out of 10 sounds correctly from either an infected or noninfected person.

"Moreover, there was no evidence that accuracy improved when participants knew the true number of infectious sounds in advance or when participants focused on how clear or disgusting they perceived the sounds," Michalak said. "Despite this poor overall accuracy, perceivers consistently reported reasonable certainty in their judgments."

Perceivers believe that what disgusts them is likely to represent a disease threat. This, Mickalak said, could potentially lead them to exhibit biases to avoid interactions with others who make disgusting but noninfectious noises.

The bottom line, according to researchers, is the next time you hear someone cough or sneeze, perhaps leave the diagnosis to the doctor.

The study's co-authors are Oliver Sng, assistant professor of psychological science at UC-Irvine, and U-M graduate student Iris Wang and U-M associate professor of psychology Joshua Ackerman.

Study: Sounds of sickness: Can people identify infectious disease using sounds of coughs and sneezes?

https://bit.ly/37riL7I

Potent tetrahydroquinolone can eliminate parasites that cause toxoplasmosis and malaria

We may soon have medicines that can make a real difference in preventing and treating active and dormant infections

Toxoplasma gondii infection is one of the most frequent parasitic infections of humans. This parasite is present in the brain of an estimated two billion people--about 40 percent of all humans on earth. It is endemic throughout the world, causing water and food-borne epidemics that result in toxoplasmosis.

This neglected, often mistreated or untreated infection, is transmitted to humans when a person eats infected undercooked meat, drinks contaminated water or is exposed to parasites in soil, usually from cat feces. Few victims recognize the exposure immediately, but the parasite causes life-long infection. It cannot presently be cured.

This disease can begin before or after birth. It can permanently damage the eyes and the brain during the initial active infection. Dormant infections can re-activate, causing severe illness or death, especially in immuno-compromised patients with cancer, autoimmune disease, AIDS or transplantation. There is no preventive vaccine.

The related tropical parasitic disease, malaria, caused by plasmodia, kills one child every 11 seconds, or about 500,000 children each year. Malaria remains an ongoing threat for travelers who visit endemic areas. Drug resistance is a significant clinical problem.

"New and improved medicines are urgently needed to prevent and cure both toxoplasmosis and malaria," said the study's senior author, Rima McLeod, MD, professor of pediatrics (infectious diseases) and ophthalmology/visual sciences at the University of Chicago Medicine and an authority on the parasite and the care of patients with toxoplasmosis.

"Many people suffer and quite a few die from these infections," she said. "Until now, no medicine has been able to eliminate the chronic, encysted form of Toxoplasma. But we may soon have medicines that can make a real difference in preventing and treating active and dormant infections."

This remarkable study, "Potent Tetrahydroquinolone Eliminates Apicomplexan Parasites," to be published June 9, 2020, in the journal *Frontiers in Cellular and Infection Microbiology*, focused on the discovery and development of new, highly effective compounds against both T. gondii and P. falciparum. The researchers discovered a lead compound that can significantly reduce or eliminate toxoplasmosis as well as malaria. These compounds are highly effective against multiple drug-resistant strains of plasmodia in vitro.

The researchers were able to dramatically improve outcomes for both diseases in mouse models. There is a relatively close phylogenetic relationship. The parasites share similarities in a molecule, known as cytochrome bc1, important for energy production.

In developing this new series of compounds, "we aimed to identify a mature lead compound with both anti-plasmodium and anti-T. gondii activity," said organic chemist Martin McPhillie, PhD, at the University of Leeds (UK). His team focused on molecules with an increased percentage of 'sp3 character.' These tend to be more three-dimensional than the more rigid 'sp2-rich' counterparts. Those with greater sp3 tend to be more specific for their protein targets. They have better physicochemical properties and can accommodate bulkier substituents (atoms taking the place of another atom or group) to minimize the effects on the human enzyme.

The scientists used enzymatic, crystallographic, cryoelectron microscopy and other in vitro and in vivo conclusive empiric studies with parasites, as well as a simple but novel nano-formulation method to find compounds that reduce or eliminate toxoplasmosis and malaria. They created and tested their lead anti-apicomplexan compound, which showed promise for treatment of these infections. This led to characterization of this compound, which revealed drug-like chemical lproperties. If utility and safety are retained and no toxicity appears in next-stage studies, this lead compound, known as JAG21 (named for James A. Gordon who synthesized it as a graduate student), "may be able to treat both T. gondii and P. falciparum human infections," said McLeod.

Colin Fishwick, PhD, dean of the Leeds School of Chemistry, and McPhillie led the team of medicinal chemists who created JAG21. Fishwick found it "absolutely stunning," that following a single, oral, low dose of JAG21, there were no surviving malarial parasites and no death of mice with otherwise lethal plasmodia infections. Mark Hickman, PhD, at Walter Reed Army Institute of Research, noted that JAG21 "has the potential to prevent and cure all three life-cycle stages of malaria."

Teams from The University of Strathclyde and UChicago found that their compound eliminated 100 percent of the active form and more than 95 percent of the previously untreatable encysted Toxoplasma parasites in mice. They also found another compound that improves efficacy of JAG21.

A few residual organisms remained after JAG21 treatment of long-established infections. UChicago scientists, working with Hernan Lorenzi at the J. Craig Venter Institute, probed for mechanisms that could eliminate potential remaining organisms. They found that different "persister stasis-like organisms" of T. gondii, grown in human brain stem cells, use a distinct genetic pathway to survive. This pathway has similarities to one recently identified in hypnozoites, a form of dormant plasmodia.

Such critical differences in gene expression sustain these novel life-cycle stages of Toxoplasma, which JAG21 can only partially inhibit in an immune-compromised mouse model. These studies point to genes that are molecular targets for new methods to eliminate the few remaining dormant organisms. Targeting these can form the basis of a companion medicine for JAG21. "The impact of these findings will be felt," said the U.Kentucky's Anthony Sinai.

Robert Prud'homme and graduate student Kurt Ristroph at Princeton University developed a method to make an oral formulation of JAG21 that is stable for months. Ying Zhou, in the McLeod group, found that this formulation of JAG21 given orally to mice--once daily for 3 days--is highly effective, even against large amounts of extremely virulent Toxoplasma.

"JAG21," the authors agree, "has the potential to become an orally administered medicine, or part of a combination, that is curative for toxoplasmosis and is a single-dose prevention and cure for malaria." If utility and safety are retained and no toxicity appears in the next series of studies, this compound may become suitable for treatment of T. gondii and P. falciparum infections. "JAG21," the team added, "has real promise."

Authors working on this study were Rima McLeod, Ying Zhou, Chris Weber, Scott Biering, Farida Hakim, Kamal El Bissati, Sarah Dovgin, Joseph Lykins, Seungmin Hwang and Cong Hua of the University of Chicago; Colin Fishwick, Martin McPhillie, James Gordon, Stephen Muench, Rachel Johnson and Heather Darby of University of Leeds; Craig Roberts, Stuart Woods, Kerrie Hargrave and Lucy Roberts of University of Strathclyde; Svetlana Antonyuk and Kangsa Aporndanai of University of Liverpool; Giancarlo Biagini and Richard Priestley of Liverpool School of Tropical Medicine; Jitender Dubey of USDA; Mark Hickman, Quigi Li and Patty Lee of Walter Reed Army Institute of Research; Silvia Moreno and Zhu-hong Li of University of Georgia; Anthony Sinai of University of Kentucky; Hernan Lorenzi of J. Craig Venter Institute; and Robert Prud'homme and Kurt Ristroph of Princeton University.

https://bbc.in/2B4Gfn8

Coronavirus came to UK 'on at least 1,300 separate occasions'

Coronavirus was brought into the UK on at least 1,300 separate occasions, a major analysis of the genetics of the virus shows.

By James Gallagher Health and science correspondent

The study, by the Covid-19 Genomics UK consortium (Cog-UK), completely quashes the idea that a single "patient zero" started the whole UK outbreak.

The analysis also finds China, where the pandemic started, had a negligible impact on cases in the UK.

Instead those initial cases came mostly from European countries.

The researchers analysed the genetic code of viral samples taken from more than 20,000 people infected with coronavirus in the UK.

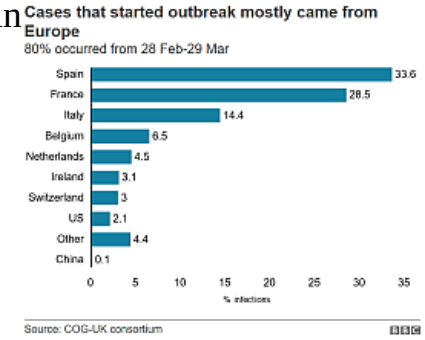
Then, like a gigantic version of a paternity test, the geneticists attempted to piece together the virus's massive family tree.

This was combined with data on international travel to get to the origins of the UK epidemic.

They found the UK's coronavirus epidemic did not have one origin - but at least 1,356 origins. On each of those occasions somebody brought the infection into the UK from abroad and the virus began to spread as a result.

"The surprising and exciting conclusion is that we found the UK epidemic has resulted from a very large number of separate importations," said Prof Nick Loman, from Cog-UK and the University of Birmingham. "It wasn't a patient zero," he added.

The study showed that less than 0.1% of those imported cases came directly from China. Instead the UK's coronavirus epidemic was largely initiated by travel from Italy in late February, Spain in early-to-mid-March and then France in mid-to-late-March.



"The big surprise for us was how fluid the process was, the rate of and source of virus introduction shifted rapidly over the course of only a few weeks," said Prof Oliver Pybus, from the University of Oxford.

"This happened later than perhaps we would have expected," added Prof Loman.

The study estimates 80% of those initial cases arrived in the country between 28 Feb and 29 March - the time the UK was debating whether to lockdown. After this point, the number of new imported cases diminished rapidly.

The earliest one could be traced back to the beginning of February, but it is possible there were cases even earlier that could not be picked up by the analysis.

The study also says the controversial football match between Liverpool and Atletico Madrid, on 11 March, probably had very little impact on bringing the virus into the country.

An estimated 3,000 fans flew in from Spain to watch the game, but there were 20,000 people flying in from Spain every single day in mid-March. "[It] shows that individual events such as football matches likely made a negligible contribution to the number of imports at that time," the study says.

The imported cases each started off a chain of transmission where the virus is passed from one person, to the next, to the next and so on. However, the study shows lockdown has massively disrupted the spread of the virus.

"If there's good news here, these chains of transmission were and are being suppressed and going extinct as a result of social distancing and we continue to see that now," Prof Loman said.

https://bit.ly/3e2eTMY

Newly synthesized fungal compound can switch on a self-destruct button for cancer

Leading organic chemists synthesize fungal molecule capable of reactivating the self-destruct gene in aggressive cancer cells

All human body cells have a certain lifespan, during which they perform their essential duties. At the end of this lifespan, they reach senescence and-no longer able to perform those duties-die. This suicidal death is programmed into their genes through a process called *apoptosis*, causing them to self-destruct in order to make way for fresh, young, and healthy cells to replace them.

Mutations in a special gene called p53 can sometimes interfere with this process. Caused by aging, ultraviolet light, and various mutagenic compounds, these mutations can disable the apoptosis gene, resulting in "zombie" cells that refuse to die and continue to multiply, spreading the disabled gene and replacing healthy working cells with undying, rapidly growing tumors. This is the

disease that we call cancer, and it takes many forms depending on which body cells develop the mutations.

Previously, scientists identified an anticancer compound called *FE399* in a species of filamentous fungus called *Ascochyta*, which is often found afflicting common food crops such as cereals. The compound is a specific group of *depsipeptides*, a type of amino acid group, and was shown to induce apoptosis in cancerous human cells, particularly colorectal cancer, while they are still *in vitro*, proving its worth as an anti-cancer chemical.

Unfortunately, due to a variety of chemical complexities, the *FE399* compound is not easy to purify, which hindered any plans for its widespread applications in cancer treatment. It was thus clear that extracting *FE399* from the fungi naturally would not be a commercially feasible method, and despite the promise of a powerful anticancer drug, research into this particular compound was stalled.

The promise of a new anticancer treatment was tempting, however, and Prof Isamu Shiina, along with Dr Takayuki Tonoi, and his team from the Tokyo University of Science, accepted the challenge. "We wanted to create a lead compound that could treat colon cancer, and we aimed to do this through the total synthesis of *FE399*," says Prof Shiina. Total synthesis is the process of the complete chemical synthesis (production) of a complex molecule using commercially available precursors, allowing mass production. The results of their extensive studies will be published in the *European Journal of Organic Chemistry*.

The team figured that first, the structure of the depsipeptide would need to be identified. This was simple and could be easily performed using commercially available and inexpensive materials. Following this simple start, the subsequent procedures required many steps and resulted in some small failures when isomers were unsuccessfully isolated.

However, the team was rewarded for their efforts when, in a major breakthrough, their mass spectrometry and nuclear magnetic resonance studies confirmed that a trio of spots on a plate showed identical chemical signature to the known formula of *FE399*, meaning that they were able to successfully recreate *FE399* synthetically.

Their technique was found to have an overall yield of 20%, which is quite promising for future large-scale production plans. "We hope that this newly produced compound can provide an unprecedented treatment option for patients with colorectal cancer, and thus improve the overall outcomes of the disease and ultimately improve their quality of life," states Prof Shiina.

Further research is needed to test the efficiency of *FE399* in the treatment of other solid and blood-based cancers, and before mass production, the biological activities and structure of the *FE399* molecule will need to be evaluated. But for now, the team from Tokyo University of Science are thrilled with their findings, and are positive that their research will help to improve treatments and therapies for patients with colorectal cancer.

Funding information

This study was partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

https://bit.ly/3hrSZVu

An aspirin a day keeps the bowel doctor away

A regular dose of aspirin to reduce the risk of inherited bowel cancer lasts at least 10 years after stopping treatment, research has revealed.

The international trial - known as CAPP2 - involved patients with Lynch syndrome from around the world and revealed that two aspirins a day, for an average of two and a half years, reduced the rate of bowel cancer by half.

The study, led by experts at the Universities of Newcastle and Leeds, UK, published in *The Lancet* today, is a planned double blind 10 year follow-up, supplemented in more than half of recruits with comprehensive national cancer registry data for up to 20 years.

Supports national guidance

The findings of the study further strengthens the National Institute for Health and Care Excellence (NICE) recommendation on taking daily aspirin for those at high risk and supports wider use of aspirin to prevent cancer.

Based on the preliminary five year data from the CAPP2 trial, NICE recommended that aspirin should be offered for the prevention of bowel cancer in adults with Lynch syndrome.

Professor Sir John Burn, from Newcastle University and Newcastle Hospitals NHS Foundation Trust, who led the research, said the new findings further support this important guidance.

He said: "I had an idea 30 years ago that people with a genetic predisposition to colon cancer could help us to test whether aspirin really could reduce the risk of cancer.

"Patients with Lynch syndrome are high risk and this offered statistical power to use cancer as an endpoint - they are like the canaries in the mine who warned the miners that there was gas.

"It took a long time to start the trial and to recruit enough people in 16 countries, but this study has finally given us an answer.

"Two aspirins a day for a couple of years gives protection that lasts more than 10 years and the statistical analysis has become much stronger with time. "For people at high cancer risk, the benefits are clear - aspirin works. Our new international trial, CaPP3, will see if smaller doses work just as well."

Findings showed that when all original recruits were included in the study, those on aspirin had 42% fewer colon cancers. Among those who took the aspirin for a full two years, there were 50% fewer colon cancers.

The study involved 861 patients with Lynch syndrome, which affects about one in 200 people in the population. These people have a genetic problem with DNA repair, making them at much higher risk of cancers such as bowel and womb.

A group of 427 were randomised to aspirin continuously for two years and 434 were allocated to a placebo and then they were all followed for 10 years. Out of those given two aspirins each day (600mg) there were 18 fewer colon cancers, representing a drop of 42.6%.

When all 163 Lynch syndrome cancers are included in the analysis - such as cancer of the endometrium or womb - there was an overall reduced risk of cancer of 24% in those taking aspirin, or 37% in those who took aspirin for the full two years.

Historic background

Between 1999 and 2005 participants began either taking two aspirins every day for two years or a placebo.

At the end of the treatment stage in 2007 there was no overall difference between those who had taken aspirin and those who had not. However, the research team anticipated a longer term effect and designed the study for continued follow-up.

By 2010 there had been 19 new bowel cancers among those who had received aspirin and 34 among those on placebo. The incidence of cancer among the group who had taken aspirin had halved - and the effect began to be seen five years after patients starting taking the aspirin.

Professor Sir John said: "Aspirin has a major preventative effect on cancer but this doesn't become apparent until at least four years later. With the help of these dedicated volunteers we have learned something of value to us all.

"Before anyone begins to take aspirin on a regular basis they should consult their doctor first as aspirin is known to bring with it a risk of stomach complaints, including ulcers and bleeding.

"However, if there is a strong family history of cancer then people may want to weigh up the cost and health benefits of taking aspirin for at least two years."

The team are now leading a new international trial, CaPP3, with more than 1,800 people with Lynch syndrome enrolled to look at whether smaller, safer doses of aspirin can be used to help reduce the cancer risk.

The research is funded by Cancer Research UK, NIHR, Bayer Pharma AG and the Barbour Foundation.

Reference

Double Blind Randomised Placebo Controlled Trial Of Cancer Prevention With Aspirin In Hereditary Colorectal Cancer (Lynch Syndrome): Planned 10 Year Follow-Up And Registry Based 20 Year Data In The CAPP2 Study. John Burn et al. The Lancet.

https://bit.ly/2Y0xJPq

Three stages to COVID-19 brain damage identified by top *neurologists in Journal of Alzheimer Disease paper*

Baseline MRIs encouraged for COVID patients

WASHINGTON, DC - The *Journal of Alzheimer's Disease* has just published a paper with a comprehensive review of the COVID-19's effect on the nervous system which classifies brain damage caused by COVID-19 into three stages. One of the authors, nationally-recognized neurologist Dr. Majid Fotuhi, MD, PhD, who is the medical director of NeuroGrow Brain Fitness Center in Northern Virginia and an affiliate staff at Johns Hopkins Medicine, encourages the adoption of this three-stage classification, calls for more research on COVID's long-term effects on the brain, and stresses the need for patients to receive a brain MRI before leaving the hospital.

"We are learning that a significant number of hospitalized COVID-19 patients have various degrees of brain impairment. As a medical community, we need to monitor these patients over time as some of them may develop cognitive decline, attention deficit, brain fog, or Alzheimer's disease in the future. There is a lot we can do to promote brain healing in COVID-19 patients, but first we must understand the nature and severity of their neurological deficits. At the patient level, getting a baseline MRI before leaving the hospital is imperative so that we have a starting point to evaluate and treat them," explained Fotuhi.

In the just published paper, Dr. Fotuhi and his colleagues warn about neurological issues in patients who suffer from COVID-19, including stroke, seizures, confusion, dizziness, paralysis, and/or coma. Already, two dozen case reports are revealing the impact of COVID-19 on the brains of patients. In fact, one study from Wuhan, China, showed that 45% of patients with severe COVID-19 illness experience marked neurological deficits. Another study from France showed 84% of ICU patients with COVID-19 have positive abnormalities on their neurological examination, and that 15% of patients who leave the ICU have residual "dysexecutive function," which involves poor attention and difficulty with decision-making and controlling behavior.

The paper proposes the adoption of a three stage "NeuroCovid" classification scheme to provide a basis from which to build on future hypotheses and investigations regarding SARS-Cov2 and the nervous system. These stages include:

- ***NeuroCovid Stage I: The virus damage is limited to epithelial cells of nose and mouth and the main symptoms include transient loss of smell and taste.***
- ***NeuroCovid Stage II: The virus triggers a flood of inflammation, called cytokine storm, which begins in the lungs and travels in the blood vessels throughout all body organs. This cytokine storm leads to the formation of blood clots which cause small or large strokes in the brain.***
- ***NeuroCovid Stage III: An explosive level of cytokine storm damages the blood brain barrier, the protective insulation layer in blood vessels of the brain. As a result, blood content, inflammatory***

markers, and virus particles invade the brain and patients develop seizures, confusion, coma, or encephalopathy.

Fotuhi points out that many patients with COVID-19 may have no noticeable neurological symptoms at first; but in some cases, patients may present with neurological symptoms even before they have fever, cough, or shortness of breath. In addition to having an MRI while at the hospital, he stresses that patients will need to be monitored in a few months after their hospitalization.

"Our experience with previous forms of coronaviruses suggest that in the long-term patients may develop depression, insomnia, Parkinson's disease, memory loss, or accelerated aging in the brain," elaborated Fotuhi. "For those recovering from COVID-19, I recommend regular exercise, eating a heart healthy diet, reducing stress, and improving sleep; these are critical ways patients can rejuvenate their brain and minimize having poor outcomes in the future."

These interventions, along with targeted brain training and neurofeedback therapy, are the main features of Dr. Fotuhi's 12-week Brain Fitness Program. As published in the Journal of Prevention of Alzheimer's Disease (2016), 84% of elderly with cognitive impairment who complete this brain rehabilitation program gain improvements in their brain function and many of them experience growth in the parts of their brain for learning and memory. These findings were similar for patients who gained recovery from their persistent post-concussion syndrome. The program will now be tailored for patients suffering from post-COVID neurological issues.

A Harvard- and Johns Hopkins-trained neurologist and neuroscientist, Dr. Fotuhi is widely regarded as an authority in the field of memory, Alzheimer's Disease, concussion treatment, ADHD, and increasing brain vitality at any age.

https://bit.ly/2C5erQ7

A compound unlike any other

A compound discovered in the gills of wood-eating clams could be the solution to a group of parasites responsible for some of the world's most common infections.

That compound is tartrolon E, a byproduct of bacteria that help shipworms, a group of saltwater clams, digest the wood they eat.

According to research recently published in *PLOS Pathogens*, the compound, unlike any other, is proven to kill causal parasites for malaria, toxoplasmosis, cryptosporidiosis, theileriosis and babesiosis.

"There are compounds that work against the individual parasites, but to find one that works against this entire group, that is what made this unique," said Roberta O'Connor, an associate professor in Washington State University's Veterinary Microbiology and Pathology unit, and first author on the paper.

While there are already effective drugs for many of the parasites mentioned here, O'Connor said this group of parasites, called apicomplexans, readily develops drug resistance. "Development of new, effective drugs against apicomplexan parasites is an ongoing need for human and veterinary medicine," she said.

One of those parasites in need of a more effective remedy is Cryptosporidium. Cryptosporidium, a waterborne zoonotic parasite, is a major cause of diarrhea in children, immunocompromised patients, and in newborn animals worldwide. The parasite infects millions of humans and agricultural animals annually.

In addition to killing this class of parasites in vitro, tartrolon E was able to kill Cryptosporidium in newborn mice.

Beginning this summer, WSU researchers will test the compound against Cryptosporidium in lambs.

Currently, nitazoxanide is the only drug approved by the Food and Drug Administration to treat cryptosporidiosis.

"Nitazoxanide doesn't work well for those [patients] who are immunocompromised or malnourished and those are the people most vulnerable to Cryptosporidium," O'Connor said.

O'Connor is the principal investigator on the study which will characterize the specific effects of tartrolon E on Cryptosporidium parasites. Villarino will lead the pharmacokinetics portion of the study in immunocompromised mice to further assess tartrolon E's effectiveness and optimal dose regimens.

The research is made possible by a recently awarded 5-year, $1.6 million grant from the National Institutes of Health. "We will define how the drug behaves in the body and how much of the drug is needed to control Cryptosporidium infection," Villarino said. "We want the maximum effect with minimal adverse effects."

This aspect of the research on the compound is a key component for drug development. "This could have a significant impact on human and veterinary medicine because there is no other drug that can effectively treat this condition," Villarino said.

O'Connor and Villarino are hopeful tartrolon E will lead to a clinically developed drug but they know it is a long way to get there. "Tartrolon E is obviously hitting some system that is common to [all] these parasites," O'Connor said. "Even if this compound isn't successful, if we can determine the mechanism, we will have identified a common drug target for all these parasites."

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

Why children avoid the worst coronavirus complications might lie in their arteries

Evidence is mounting that healthy blood vessels protect children from serious effects of COVID-19, such as stroke.

David Cyranoski

Since the coronavirus outbreak began, scientists have been trying to work out why children are much less likely than adults to experience severe complications from the infection. Now research suggests that the answer might lie in children's healthy blood vessels.

Children make up only a small proportion of those infected by SARS-CoV-2, the virus that causes COVID-19. A large survey by the US Centers for Disease Control and Prevention in Atlanta, Georgia, found that children aged 17 and under, who make up 22% of the US population, account for fewer than 2% of confirmed COVID-19 infections across the United States. And, of 2,572 children included in the survey, only 5.7% went to hospital and only three died.

Several theories have been proposed to explain why children aren't getting so ill. These include the possibility that they have a stronger and more effective initial immune response to the virus than adults do, and that they might have some immunity from recent exposure to similar viruses. But a growing number of researchers think that the difference between adults and children might be the condition of their blood vessels.

Many adults with serious COVID-19 experience clotting in their blood vessels, which leads to heart attacks or strokes. The clotting seems to be linked to a malfunctioning endothelium, the smooth tissue that lines blood vessels and normally prevents clotting, says Frank Ruschitzka, a cardiologist at the University Hospital Zurich in Switzerland. Normally, blood clots form only to stop bleeding from an injury, but if the endothelium is damaged, clots can also form.

Ruschitzka and colleagues have found that SARS-CoV-2 can infect endothelial cells, which are found throughout the body. In a study of three people with COVID-19, two of whom died, Ruschitzka's team found that SARS-CoV-2 had infected the patient's endothelium and caused inflammation and signs of clotting [1]. The study was small so such complications will need to be investigated further, but problems with the endothelium seem to be involved in

most cases of COVID-19 that progress to severe or fatal disease in adults, he says.

This theory could also explain why people with conditions that compromise the endothelium, such as diabetes and hypertension, are at a greater risk of serious COVID-19, says Marcel Levi, a haematologist at University College Hospital in London.

Perfect condition

Endothelium is typically in much better condition in children than adults. “A kid’s endothelium is set up perfectly and then just deteriorates with age,” says Paul Monagle, a paediatric haematologist at the Melbourne Children’s Campus.

Monagle and others think that children’s blood vessels are able to withstand a viral attack than adults. Further support for this theory is the observation that few children with COVID-19 present with excessive clotting and damaged vessels, he says.

Monagle is trying to understand what happens when the virus enters endothelial cells. He thinks it likely disrupts communication between the cells, the platelets and plasma components involved in clotting, and that this communication breakdown leads to excess clots forming.

He has launched two experiments to try to better understand this mechanism and see whether there is something protective about kids’ blood vessels that makes them less likely to produce excess clots in response to viral infection. In the first experiment, his team will try to recreate conditions inside the blood vessels of children and adults in the lab. They will take cultured endothelial cells infected with SARS-CoV-2 and bathe them in plasma from three sources — children, healthy adults, and adults with vascular disease. By comparing how the infected cells interact with the three different types of plasma, they should be able to see what makes the signalling in the vessels go awry.

Monagle hopes that studying samples from children will offer clues about what’s going wrong in some adults. “If we understand what happens to children, we could tweak adults to make them more child-like,” he says.

In a second experiment, the team will analyse plasma from children and adults with COVID-19, which contains proteins released by damaged endothelial cells, to identify possible markers of disease.

doi: 10.1038/d41586-020-01692-z

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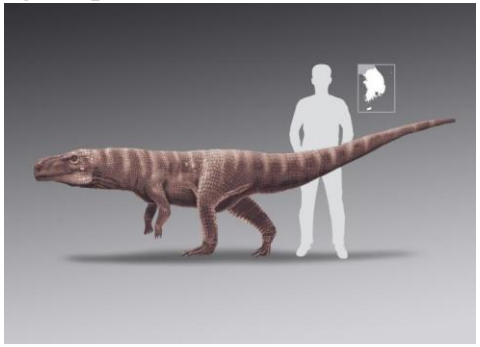
https://bit.ly/2YuKFvz

New discovery of giant bipedal crocodile footprints in the cretaceous of Korea

CU Denver researcher Marin Lockley was a member of the team that found the well-preserved footprints

A new study released today in *Scientific Reports* announced the surprising discovery of abundant, well-preserved 110-120-million-year-old footprints, belonging to a large bipedal ancestor of modern-day crocodiles from the Lower Cretaceous Jinju Formation of South Korea. The team of palaeontologist trackers that made the discovery includes researchers from Korea, Australia, and University of Colorado Denver professor, Martin Lockley.



Reconstruction of a 4 meter (13 foot) long bipedal crocodile based on trackways from the Cretaceous of Korea. **Credit: Anthony Romilio**

While palaeontologists knew that some crocodiles from the "age of dinosaurs" were more adapted to life on land than their modern relatives, these were small animals about one meter long with footprints showing they walked on all fours.

"It shocked us to learn that the trackways represent bipedal animals 3-4 meters long," said team leader Professor Kyung Soo Kim, Chinju National University of Education.

The team named the 18-24 cm-long tracks *Batrachopus grandis* emphasizing the large size in comparison with much older and smaller 2-3 long cm tracks of the *Batrachopus* type, commonly found in the Jurassic of North America.

"Nobody expected such large bipedal crocs," said Martin Lockley, a University of Colorado professor who has been studying fossil footprints in Korea for 30 years. "The Jinju Formation is so rich in tracks; you can read the entire ecology."

The discovery of well-preserved tracks is important to palaeontologist trackers because they show details of skin impressions as clear as if made yesterday. Tracks also read the pattern of pads, showing foot bone structure and the tell-tale narrowness of trackways which show a bipedal gait, different from the sprawling posture of modern crocodiles. There has even been evidence from parallel trackways that show they may have travelled in social groups, just like their dinosaur cousins.

Among with the remains of some of the oldest terrestrially adapted crocodiles, are large Triassic species, more than 200 million years old, that some palaeontologists think may have been bipedal, based on anatomy.

"The Korean trackways prove this hypothesis, at least for the Cretaceous Period," said co-author of the study, Anthony Romilio. "It also proves this adaptation was effective for millions of years, even with big fierce dinosaurs running around."

The new study has also solved a tracking mystery dating back to 2012, when some poorly preserved tracks of a bipedal animal were first found in another South Korean rock unit, described as "enigmatic." There was debate over whether the giant pterosaurs were bipeds, quadrupeds or possibly even pterosaurian or human.

https://bit.ly/3e7lrKA

Discovery of oldest bow and arrow technology in Eurasia

New archaeological research demonstrates earliest projectile technology in the tropical rainforests of Sri Lanka

The origins of human innovation have traditionally been sought in the grasslands and coasts of Africa or the temperate environments of Europe. More extreme environments, such as the tropical rainforests of Asia, have been largely overlooked, despite their deep history of human occupation. A new study provides the earliest evidence for bow-and-arrow use, and perhaps the making of clothes, outside of Africa ~48-45,000 years ago -in the tropics of Sri Lanka.

The island of Sri Lanka in the Indian Ocean, just south of the Indian subcontinent, is home to the earliest fossils of our species, Homo sapiens, in South Asia. It also preserves clear evidence for human occupation and the use of tropical rainforest environments outside of Africa from ~48,000 to 3,000 years ago - refuting the idea that these supposedly resource-poor environments acted as barriers for migrating Pleistocene humans. The question as to exactly how humans obtained rainforest resources - including fast-moving food sources like monkeys and squirrels - remains unresolved.

Fa-Hien Lena has emerged as one of South Asia's most important archaeological sites since the 1980s, preserving remains of our species, their tools, and their prey in a tropical context. **Langley et al., 2020**

In this new study, published in *Science Advances*, an international team of researchers from the Max Planck Institute for the Science of Human History (MPI-SHH) in Germany, Griffith University in Australia and the Department of Archaeology, Government of Sri

Lanka, present evidence for the earliest use of bow-and-arrow technologies by humans anywhere outside of Africa. At ~48,000 years old, these tools are earlier than the first similar technology found in Europe. Clear evidence for use on the preserved bone arrowheads shows that they were likely used for hunting difficult-to-catch rainforest prey. Not only that, but the scientists show that other bone tools may have been used for making nets or clothing in tropical settings, dramatically altering traditional assumptions about how certain human innovations were linked with specific environmental requirements.

Hunting in the open and sheltering from the cold?

European cultural products in the form of cave art, amazingly detailed bone carvings, bone tool technologies, and tailored clothing have been frequently held up as the pinnacle of Late Pleistocene human cultural development. There, symbolic and technological innovations have been seen as key survival mechanisms equipping expanding populations to face cold northern climates. Meanwhile, discoveries of older bow-and-arrow technology and artistic or symbolic behaviors in open grassland or coastal settings in Africa have framed 'savannah' and marine environments, respectively, as key drivers behind early hunting and cultural experiments by Pleistocene humans in their evolutionary homeland.

The team found clear evidence for the production of colored beads from mineral ochre and the refined making of shell beads traded from the coast, at a similar age to other 'social signaling' materials found in Eurasia and Southeast Asia, roughly 45,000 years ago. **Adapted from Langley et al., 2020**

As co-author of the new study, Patrick Roberts of the MPI-SHH argues that "this traditional focus has meant that other parts of Africa, Asia, Australasia, and the Americas have often been side-lined in discussions of the origins of material culture, such as novel projectile hunting methods or cultural innovations associated with our species." Nevertheless, the last twenty years have highlighted how Pleistocene humans occupied and adapted to a variety of extreme environments as they migrated beyond Africa, including deserts, high-altitude settings and tropical rainforests such as those of Sri Lanka.

A tropical home

The new study saw scientists turn to the beautifully preserved material culture from the cave of Fa-Hien Lena, deep in the heart of Sri Lanka's Wet Zone forests. As co-author Oshan Wedage, PhD at MPI-SHH, states, "Fa-Hien Lena has emerged as one of South Asia's most important archaeological sites since the 1980s, preserving remains of our species, their tools, and their prey in a tropical context." Some of the main finds from the site include remarkable single and doubled pointed bone tools that scientists had suspected were used in the exploitation of tropical resources. Direct proof had been lacking, however, in the absence of detailed high-powered microscopic analysis.

Michelle Langley of Griffith University, the lead author of the new study, is an expert in the study of microscopic traces of tool use and the creation of symbolic material culture in Pleistocene contexts. Applying cutting edge methods to the Fa-Hien Lena material confirmed the researchers' hypothesis. As Langley states, "the fractures on the points indicate damage through high-powered impact - something usually seen in the use of bow-and-arrow hunting of animals. This evidence is earlier than similar findings in Southeast Asia 32,000 years ago and is currently the earliest clear evidence for bow-and-arrow use beyond the African continent."

The evidence for early human innovation did not stop there. Applying the same microscopic approach to other bone tools, the team identified implements which seem to have been associated

with freshwater fishing in nearby tropical streams, as well as the working of fiber to make nets or clothing. "We also found clear evidence for the production of colored beads from mineral ochre and the refined making of shell beads traded from the coast, at a similar age to other 'social signaling' materials found in Eurasia and Southeast Asia, roughly 45,000 years ago," says Michelle Langley. Together, this reveals a complex, early human social network in the tropics of South Asia.

A flexible toolkit for new hunting grounds

The new study highlights that archaeologists can no longer link specific technological, symbolic, or cultural developments in Pleistocene humans to a single region or environment. "The Sri Lankan evidence shows that the invention of bows-and-arrows, clothing, and symbolic signaling occurred multiple times and in multiple different places, including within the tropical rainforests of Asia," says co-author Michael Petraglia of the MPI-SHH. In addition to insulation in cold environments, clothes may have also helped against tropical mosquitoes, "and instead of just hunting large grassland mammals," adds zooarchaeologist Noel Amano, another MPI-SHH co-author, "bows and arrows helped humans procure small, tree-dwelling primates and rodents."

While archaeologists have long focused on the uniqueness of European markers of behavioural modernity, the new study is part of a growing awareness that many regions of the world saw extraordinary and complex new technologies emerge at the end of the Palaeolithic.

"Humans at this time show extraordinary resourcefulness and the ability to exploit a range of new environments," notes Nicole Boivin, Director at the MPI-SHH and study coauthor. "These skills enabled them to colonize nearly all of the planet's continents by about 10,000 years ago, setting us clearly on the path to being the global species we are today."

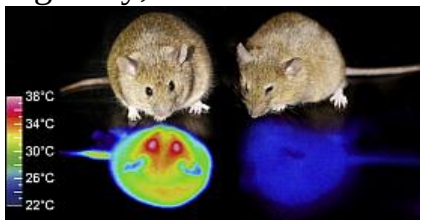
https://bit.ly/2UHqBFg

Hibernation in mice: Are humans next?

Researchers at the University of Tsukuba and RIKEN in Japan spark a hibernation-like state in mice--a species that does not naturally hibernate

Tsukuba Japan -- In Sci-Fi movies, astronauts often enter an inactive state in "hibernation chambers" to cross the vastness of space. This could cut down on the required amount of food and oxygen and to prevent serious side effects from low gravity, such as muscle wasting in zero-G condition.

A state of unconsciousness could also potentially minimize psychological challenges in space. Could humans hibernate in the future?



Posture of mouse during QIH. We induced QIH, a synthetic hibernation-like state, to mouse and took pictures along with infrared imaging. Left, control mouse. Right, QIH mouse (48hr after CNO injection). We made mirror-images of infrared images, and made compositions with photos **University of Tsukuba**

Why do some animals hibernate while others do not? Do all animals have the potential to hibernate even if they never do so in nature? Researchers from the University of Tsukuba in Japan opened the door to answering these questions by finding specific cells in the mouse brain that can trigger a hibernation-like state when activated. The study was published in the scientific journal *Nature*.

Animals usually enter hibernation when food becomes scarce in the winter. Their metabolism slows down, and their body temperature drops to a new set-point. This is like lowering the temperature on your thermostat in the winter--it reduces the amount of energy needed to maintain the body. Along with a slower metabolism and a new set-point comes slower heart rate, weaker breathing, and less

brain activity. Importantly, when animals come out of hibernation, their body and organs are healthy, even if they have lost a little weight.

Even though mice do not hibernate, researchers led by Takeshi Sakurai at the University of Tsukuba and Genshiro Sunagawa at the RIKEN Center for Biosystems Dynamics Research show that activating a specific type of cell in the mouse brain--dubbed Q neurons--caused them to enter a hibernation-like state for several days. "The mice exhibited distinctive qualities that met the criteria for hibernation," notes Sakurai. "In particular, the body temperature set-point lowered from about 96.8°F [36°C] to about 81°F [27°C], and the body functioned normally to maintain a lower body temperature around 22°C, even when the surrounding ambient temperature was dramatically reduced." The mice also showed all the signs of a reduced metabolism that are common during hibernation, including reduced heart rate, oxygen consumption, and respiration.

Being able to send mice into a hibernation-like state for days simply by artificially exciting Q neurons was somewhat unexpected. "Even more surprising," says first author Tohru Takahashi, "is that we were able to induce a similar hypometabolic state in rats, a species that neither hibernates nor has daily torpor." Although we do not know the answer yet, the possibility that humans also have Q neurons that can be used to induce a similar state is tantalizing.

"People might not want to hibernate for the same reasons as animals," explains Sunagawa. "But there are medical reasons for wanting to place people in suspended animation, such as during emergency transport or critically ill conditions as in severe pneumonia, when the demand for oxygen cannot meet the supply."

Sparing oxygen is not only for medicine. "In the future," Sakurai added, "we may put human in a hibernation-like state for missions to Mars and beyond."

https://bit.ly/2UK63vI

New biomaterial has potential to repair damaged bone with lower risk of inflammation

Could accelerate bone regeneration by promoting an immune response that encourages repair and lowers the risk of inflammation

Scientists at RCSI University of Medicine and Health Sciences have developed a new biomaterial that has the potential to accelerate bone regeneration by promoting an immune response that encourages repair and lowers the risk of inflammation.

The study, conducted by researchers at RCSI Tissue Engineering Research Group (TERG) and AMBER, the SFI Research Centre for Advanced Materials and BioEngineering Research, is published in *Acta Biomaterialia*

The researchers have developed a technology that is a combination of nanoparticles and a collagen-based biomaterial called a scaffold, specifically designed by RCSI TERG that can be surgically implanted to aid bone tissue repair. The material allows for the delivery of a microRNA silencer, a molecule capable of influencing the way our cells function.

In laboratory conditions, researchers successfully demonstrated that damaged bone tissue is restored as the particular microRNA delivered by the biomaterial works to increase cells responsible for bone repair. The technology also assists in promoting a pro-repair immune system response, lowering the risk of inflammation and other complications.

"The results of our research are a promising step towards improving health outcomes for patients with fractures that fail to repair naturally or have degenerative bone diseases such as osteoporosis, although further pre-clinical and clinical trials are still required before the technology could be used to treat humans," said Dr

Caroline Curtin, Lecturer in Anatomy and Regenerative Medicine at RCSI.

"We are confident that this biomaterial system will have several potential applications beyond bone repair, as it can be tailored to deliver other therapeutic molecules that address degenerated or diseased tissue in the body. At RCSI Tissue Engineering Research Group, we are exploring these possibilities through the development of similar methods to repair articular joints like the knee and hip, and attempting to apply the microRNA delivery systems to inhibit breast cancer cell growth and other novel research," said Prof. Fergal O'Brien RCSI Director of Research and Innovation, Professor of Bioengineering and Regenerative Medicine and Deputy Director of the SFI AMBER Centre.

The research, undertaken by first author Dr Irene Mencía Castaño, is supported by Science Foundation Ireland (SFI) Research Frontiers Programme, the Advanced Materials and Bioengineering Research (AMBER) Centre through SFI and the ERC under the European Commission's Horizon 2020 Framework Programme/ERC grant agreement.

https://bit.ly/2BZHDrC

COVID-19 may trigger new diabetes, experts warn

Emerging evidence suggests that COVID-19 may actually trigger the onset of diabetes in healthy people and also cause severe complications of pre-existing diabetes.

A letter published today in the *New England Journal of Medicine* and signed by an international group of 17 leading diabetes experts involved in the CoviDiab Registry project, a collaborative international research initiative, announces the establishment of a Global Registry of new cases of diabetes in patients with COVID-19.

The Registry aims to understand the extent and the characteristics of the manifestations of diabetes in patients with COVID-19, and the best strategies for the treatment and monitoring of affected patients, during and after the pandemic.

Clinical observations so far show a bi-directional relationship between COVID-19 and diabetes. On the one hand, diabetes is associated with increased risk of COVID-19 severity and mortality. Between 20 and 30% of patients who died with COVID-19 have been reported to have diabetes. On the other hand, new-onset diabetes and atypical metabolic complications of pre-existing diabetes, including life-threatening ones, have been observed in people with COVID-19.

It is still unclear how SARS-Cov-2, the virus that causes COVID-19, impacts diabetes. Previous research has shown that ACE-2, the protein that binds to SARS-Cov-2 allowing the virus to enter human cells, is not only located in the lungs but also in organs and tissues involved in glucose metabolism such as the pancreas, the small intestine, the fat tissue, the liver and the kidney. Researchers hypothesise that by entering these tissues, the virus may cause multiple and complex dysfunctions of glucose metabolism. It has also been known for many years that virus infections can precipitate type 1 diabetes.

Francesco Rubino, Professor of Metabolic Surgery at King's College London and co-lead investigator of the CoviDiab Registry project, said: "Diabetes is one of the most prevalent chronic diseases and we are now realizing the consequences of the inevitable clash between two pandemics. Given the short period of human contact with this new coronavirus, the exact mechanism by which the virus influences glucose metabolism is still unclear and we don't know whether the acute manifestation of diabetes in these patients represent classic type 1, type 2 or possibly a new form of diabetes".

Paul Zimmet, Professor of Diabetes at Monash University in Melbourne, Honorary President of the International Diabetes

Federation and co-lead investigator in the CoviDiab Registry project said: "We don't yet know the magnitude of the new onset diabetes in COVID-19 and if it will persist or resolve after the infection; and if so, whether or not or COVID-19 increases risk of future diabetes. By establishing this Global Registry, we are calling on the international medical community to rapidly share relevant clinical observations that can help answer these questions".

Stephanie Amiel, Professor of Diabetes Research at King's College London and a co-investigator of the CoviDiab Registry project said: "The registry focuses on routinely collected clinical data that will help us examine insulin secretory capacity, insulin resistance and autoimmune antibody status to understand how COVID-19 related diabetes develops, its natural history and best management. Studying COVID-19-related diabetes may uncover novel mechanisms of disease."

https://wb.md/2UJy9Y5

New Global Registry Investigates COVID-19 and New-Onset Diabetes

A new global registry has been established to collect data on patients with COVID-19-related diabetes.

Miriam E. Tucker

Emerging evidence suggests that COVID-19 may actually trigger the onset of diabetes in healthy people.

A notice about the CoviDiab registry was published online June 12 in a letter to the editor in the *New England Journal of Medicine* by Francesco Rubino, MD, King's College London, UK, and a panel of diabetes experts from Europe, Australia, and the United States.

"Given the short period of human contact with this new coronavirus, the exact mechanism by which the virus influences glucose metabolism is still unclear and we don't know whether the acute manifestation of diabetes in these patients represents classic type 1, type 2, or possibly a new form of diabetes," said Rubino in a press release from his institution.

Not everyone agrees, however, that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus triggers diabetes in people who did not have it before getting COVID-19.

"There is no robust data yet to indicate that COVID-19 causes new diabetes," Riyaz Patel, MBBS, a cardiologist at University College Hospital, London, UK, told the UK Science Media Center.

Lora Heisler, PhD, of the University of Aberdeen, UK, agrees, but she said: "This registry is a great first step in trying to answer the question of...whether the diabetes is actually new...because some people may have [had] undiagnosed diabetes."

Rubino and colleagues say their goal "is to establish the extent and phenotype of new-onset diabetes that is defined by hyperglycemia, confirmed COVID-19, a negative history of diabetes, and a history of a normal glycated hemoglobin level."

Evidence for Potential Diabetogenic Effect of SARS-CoV-2 Virus

The authors point out that a bidirectional relationship has been observed between COVID-19 and diabetes. On the one hand, the presence of diabetes is associated with increased COVID-19 severity.

But in addition, new-onset type 1 and type 2 diabetes have been reported, as have severe metabolic complications of pre-existing diabetes, including diabetic ketoacidosis and hyperosmolarity requiring exceptionally high insulin doses.

One theory as to how the SARS-CoV-2 virus could trigger diabetes is through binding to angiotensin-converting enzyme 2 (ACE2) receptors in key metabolic organs and tissues, including pancreatic beta cells and kidneys.

There are also several precedents for viral triggering of ketosis-prone diabetes, including other coronaviruses.

"In the aggregate, these observations provide support for the hypothesis of a potential diabetogenic effect of COVID-19, beyond the well-recognized stress response associated with severe illness," Rubino and colleagues say.

"We don't yet know the magnitude of the new-onset diabetes in COVID-19 and if it will persist or resolve after the infection; and if so, whether or not or COVID-19 increases risk of future diabetes," added Paul Zimmet, MD, PhD, professor of diabetes at Monash University in Melbourne, Australia, and a co-lead investigator in the CoviDiab registry project.

"By establishing this global registry, we are calling on the international medical community to rapidly share relevant clinical observations that can help answer these questions," Zimmet added.

"Given the very short history of human infection with SARS-CoV-2, an understanding of how COVID-19–related diabetes develops, the natural history of this disease, and appropriate management will be helpful," say the researchers.

At a later point, the registry will be expanded to include patients with pre-existing diabetes who present with severe acute metabolic disturbance.

Rubino has reported receiving grants from Ethicon and Medtronic, personal fees from GI Dynamic, Keyron, Novo Nordisk, Ethicon, and Medtronic.

N Engl J Med. Published online June 12, 2020. Letter

https://bit.ly/2ULEq5I

Potential beginning of life simulated in lab

Did life originate underground?

Scientists at the University of Duisburg-Essen (UDE) have substantiated their theory that life could have begun deep in the Earth's crust. In their experiments, structures that were inanimate developed survival strategies within a short time.

In the beginning, there was the vesicle: A self-generated bubble similar to a soap bubble, enclosed by a membrane. It was surrounded by a liquid according to the recipe of the primeval soup, with a temperature of 40 to 80°C and increased pressure. Those are the conditions as they existed some 3.8 billion years ago and still do today—far down in the Earth's crust.

With this experimental setup, chemist Christian Mayer from the Center for Nanointegration (CENIDE) and geologist Ulrich Schreiber, also a professor at the UDE, have simulated water-filled crevices in the Earth's bowels as well as geothermal sources. In their laboratory experiment, they created and disintegrated a total of 1,500 vesicle generations within two weeks.

The researchers discovered that some vesicles survived the generation change because they had embedded certain protein precursors from the primordial soup into their membrane. This made them more stable, smaller and—most importantly—their membrane became slightly more permeable.

Forwarding functions to subsequent generations

"We concluded that this way, the vesicles were able to compensate for destructive pressure. As a survival strategy, if you will," explains Mayer. Even if such a vesicle was destroyed, the next generation took up the protein structure. In this way, it adopted a function from its predecessors—similar to classical inheritance.

Mayer and Schreiber are certain that they have at least shown the way to a preliminary stage of life. "As we have simulated in time-lapse, billions of years ago, such vesicles might have become stable enough to come to the surface during geyser eruptions," said Schreiber. Over time, other functions might have been added until the first cell was formed.

Mayer summarizes: "We suspect that this type of molecular evolution in depth took place parallel to other mechanisms or temporally displaced from them."

Mayer and Schreiber's book, "The First Cell—The Mystery Surrounding the Beginning of Life," will be published in July 2020.

https://bit.ly/3d0ySdN

Face masks don't even have to work especially well to be effective

But to stop the pandemic, they have to be combined with lockdowns.

John Timmer

Advice on whether or not to use face masks to limit the spread of the pandemic has varied from country to country, even differing by location within countries. These policies have had to balance whether there were sufficient supplies for medical personnel to divert some to the general public. And the whole issue was decided without a clear idea of whether face masks were actually effective against SARS-CoV-2.

But there has been reason to think masks would at least be somewhat effective, based on studies of the spread of droplets of material we expel while coughing or sneezing. And a recent analysis suggested a large group of individual studies collectively pointed to their effectiveness. But that analysis left a large degree of uncertainty about how effective they'd be at the population level and how face mask use would interact with other policy decisions.

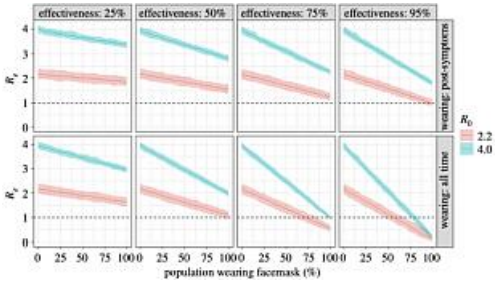
The situation left us needing population-level modeling, which a group of UK scientists has now provided. The group's model indicates that face masks don't have to be especially effective to slow the spread of SARS-CoV-2—as long as they limit the spread of the virus from infected people, they can limit the pandemic even if they make mask wearers more susceptible to infection. But to really control the pandemic, masks will have to be combined with a lockdown if we want to see the total infected population shrink.

Masks vs. virus

Mask use actually has two different functions. To a degree, it limits the ability of people who are infected to put infectious particles into the environment. And to a potentially different degree, it limits access to two of the primary routes by which those particles can reach new hosts: the mouth and nose. It's not a complete solution, as a person's eyes are still uncovered, and the degree of effectiveness will vary based on how many potentially infectious particles are filtered out. Still, even a crude mask is likely to capture many of the largest particles we produce, and those are the ones that will carry the most viruses.

There's also some uncertainty about the virus's behavior. We don't know how much of it is present in a typical droplet expelled by an infected person or how long the virus remains infectious once those particles make it to the environment. There's also some residual uncertainty about when a person becomes infectious relative to the onset of symptoms. While some of these unanswered questions don't alter the effectiveness of masks, they can influence how effective policies on mask use are.

To get around these issues, the researchers decided to model a wide range of conditions, some in which the face masks were only slightly effective and others in which they blocked much of the spread of the virus. The authors even ran models in which wearing a face mask was assumed to *increase* the chances of someone becoming infected by causing people to bring their hands to their faces to adjust the mask's fit.



***Enlarge** / Different scenarios test distinct effectiveness of masks, as well as the frequency of their use. The authors looked at high (blue) and moderate (red) infectiousness situations.*

To get at all these questions, the researchers relied on two different models. The first was something called a "branching process model" that got at the question of how effective a face mask had to be before it could influence the rate of transmission of SARS-CoV-

2, based on how many people were wearing masks. They ran this model with two different base rates of infectivity and looked at how different levels of effectiveness and use changed those rates.

In the graph above, the blue bars represent a high rate of infectivity (each infection results in four additional ones) and the second a more moderate rate (2.2 new infections for every one). Even low levels of use of ineffective masks were able to bring the rate of viral spread down toward a rate of 1, below which the pandemic would gradually stop spreading.

But for the most part, mask use alone isn't able to get there. If, as in the top row, people start wearing masks after the onset of symptoms, there are no scenarios in which face masks alone are able to stop the pandemic—even if they are 95-percent effective and everyone with symptoms wears them. By contrast, if everyone wears them all the time, even a 75-percent effective mask could possibly bring the rate of new infections down on its own.

More policies

But using face masks isn't likely to occur in a vacuum; it's going to be part of a suite of policy solutions implemented in response to the pandemic. So the authors built a second model based on a standard epidemiology approach that divides a population up into pools of susceptible, infected, and recovered people. They layered a fair bit of complexity onto this approach, splitting the population up into mask-wearers and those without, breaking out exposed, asymptomatic, and symptomatic groups and building an exposure process that took into account the formation and spread of virus-containing droplets.

This last piece of the model was essential to considering the role of masks, as they influence both the spread of these droplets into the environment and a susceptible person's exposure to them. The model also assumes that anyone who reaches the recovered state is immune to further infection—something that has yet to be confirmed.

Running the model with no face mask use and lockdowns in response to high infection levels produces what pretty much every model has seen: a large peak of infection that induces a lockdown, a recovery period in which the lockdown is relaxed, followed by an additional peak. In this model, three individual peaks are seen before sufficient immunity is reached to start slowing further waves of infections.

Assuming a face mask that's even less effective than cotton cloth is at preventing the spread of droplets, a 50-percent rate of mask use is able to delay further peaks. The second peak, for example, would start at about the same time that the population is already in lockdown under the no-mask-use scenario. At 100-percent face mask use, there's only a single wave of infections and then the pandemic starts to decline. In this scenario, infections will decline even if face masks are only 50-percent effective. With 95-percent mask use, an N95-level of protection is enough to cause the pandemic to decline.

As mentioned above, the researchers also considered a scenario where wearing masks makes people *more* susceptible to infection, as they touch their face more often because of the mask's presence. While mask wearers suffer in this scenario, the population overall still benefits under most conditions in which at least two-thirds of the population is wearing masks. That's because there are so many fewer infectious particles around that this offsets the increased susceptibility.

Models meet the real world

Right now, we just don't know enough about SARS-CoV-2 and protective gear to evaluate which of these models best reflects reality. But the models do set some reasonable bounds about what we might aim for. For example, they indicate that masks don't need

to be especially good if we get enough people wearing them and couple their use to other policy initiatives.

A few indications that mask use is working in the real world are starting to crop up. For example, an economics institute in Germany looked at the implementation of mask rules in the city of Jena, comparing it to other areas in Germany. It concluded that the rules reduced the growth of the infection rate by 40 percent. (Note that's the growth rate, not the overall rate of infection.) A non-peer-reviewed study published by PNAS found that mask use made a difference in China, Italy, and the US, although some of the data isn't entirely compelling. (Looking specifically at Figure 3A, face mask rules seem to have been put in place after infections were already trending downward.) There's nothing conclusive yet, but there's some suggestive evidence, and no signs that face mask use is making matters worse.

Proceedings of the Royal Society A, 2020. DOI: 10.1098/rspa.2020.0376 (About DOIs).

https://bit.ly/3htilCH

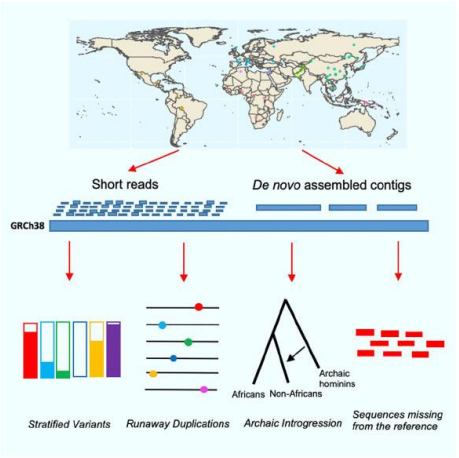
Researchers Identify 126,018 Human Genetic Variations

Comprehensive structural variation atlas for a geographically diverse set of human genomes and recovered sequences missing from the human reference sequence

A team of scientists from the Wellcome Sanger Institute, the Francis Crick Institute, and EMBL-EBI has created a comprehensive structural variation atlas for a geographically diverse set of human genomes and recovered sequences missing from the human reference sequence. Among the 126,018 structural variations discovered by the team were medically-important genes in Oceanian populations that were inherited from Denisovans, a

Structural variations are genetic changes that can encompass anything from a few to millions of base pairs of DNA. They contribute substantially to genetic diversity and are important evolutionarily and medically, but they are still understudied.

Up until now, most large-scale genetic studies have generally focused on changes affecting single base pairs of DNA.



Wellcome Sanger Institute researcher Mohamed Almarri and colleagues previously sequenced 911 genomes from 54 geographically, linguistically and culturally diverse populations from across the globe, and have now searched for structural variations in these sequences.

sister group to Neanderthals.

Almarri et al present a comprehensive analysis of structural variation in the Human Genome Diversity panel, a high-coverage dataset of 911 samples from 54 diverse worldwide populations, and identify, in total, 126,018 variants, 78% of which were not identified in previous global sequencing projects. **Image credit: Almarri et al, doi: 10.1016/j.cell.2020.05.024.**

The sequences were compared to the human reference genome to create a catalogue of structural variations, over three quarters of which were previously unknown.

The scientists then investigated how common these structural variations are in each of the 54 populations, and which of them were inherited from Neanderthals or Denisovans.

Among the 126,018 structural variations discovered were medically-important variations inherited from Denisovans in Oceanian populations from Papua New Guinea and nearby, including a high-frequency deletion in the AQR gene that plays a role in detection of viruses and regulation of antiviral immune response.

“By analyzing the genomes of understudied populations we’ve been able to find high-frequency structural variations not uncovered by previous large-scale sequencing projects,” Almarri said.

“Several of these are in medically-important genes that tell us how a population has evolved to resist a certain disease or why they might be susceptible to others.”

“This is vital knowledge and will help to ensure that treatments can be tailored to each specific population.”

Other notable structural variations were uncovered by the team that, together with existing knowledge of human evolution and the role of specific genes, shine a light on how individual populations have evolved.

The Karitiana people, who reside in modern-day Brazil, were found to carry a variation in the MGAM gene that affects starch digestion. Their diet is derived from fishing, hunting and farming, so a decrease in starch digestion is probably disadvantageous and therefore surprising. It is thought that bad luck may have concentrated this variation in the small population that survived a population crash within the last 5,000 years.

The authors also discovered novel ‘runaway duplications,’ where populations have evolved to carry multiple copies of genes.

For example, all of the African populations included in the study carried multiple copies of the HPR gene, which is associated with resistance to sleeping sickness. The highest numbers of copies — up to 9 — were carried by Central and West African populations, where the disease is most prevalent.

“This is a very valuable study showing the importance of structural variation of the human genome in the genetic diversity of humans around the world,” said Dr. Ed Hollox, a researcher at the University of Leicester who was not involved in the study. “The work supports the concept that some human adaptations to different environments are due to the loss or gain of whole genes, or parts of genes.”

“Structural variation can be challenging to find, and this study also provides a well-founded structural variation reference set which will serve as an important springboard for future studies.”

The results appear in the journal *Cell*.

Mohamed A. Almarri et al. Population Structure, Stratification, and Introgression of Human Structural Variation. Cell, published online June 11, 2020; doi: 10.1016/j.cell.2020.05.024

https://wb.md/30Glwkv

Noninvasive Ventilation May Beat Standard Oxygen for AHRF, Study Shows

Helmet or face mask noninvasive ventilation (NIV) may help patients survive acute hypoxemic respiratory failure (AHRF) or avoid endotracheal intubation, a new study shows.

Troy Brown, RN

One expert would like to see access to these technologies expanded to include outpatients as well.

"There are multiple alternatives to standard oxygen which seem to be better," lead author Bruno L. Ferreyro, MD, from the University of Toronto and Sinai Health System and University Health Network, Toronto, Canada, told *Medscape Medical News*.

"All of these interventions could be effective, but clinicians need to know that none of these interventions should delay timely intubation. Patients who need to be intubated need to be intubated.... [Delaying intubation] has been shown to be harmful for patients," he continued.

Ferreyro and colleagues' findings were published online on June 4 in *JAMA*. "The current coronavirus disease 2019 (COVID-19) pandemic has further highlighted the importance of understanding the best approach to providing respiratory support for patients with respiratory failure," the authors write.

The researchers conducted a systematic review and network meta-analysis of 25 randomized clinical trials involving 3804 participants.

The primary outcome was all-cause mortality, which was measured at the longest time point during the first 90 days after randomization.

The secondary outcome was endotracheal intubation up to 30 days.

Other secondary outcomes were "patient comfort, dyspnea scores, intensive care unit and hospital lengths of stay, and 6-month mortality," the authors explain.

Treatment with helmet NIV (risk ratio [RR], 0.40; absolute risk difference, –0.19; low certainty) and face mask NIV (RR, 0.83; absolute risk difference, –0.06; moderate certainty) were linked to a lower risk for mortality compared with standard oxygen therapy (21 studies; 3370 patients).

High-flow nasal oxygen (RR, 0.87; absolute risk difference, –0.04; moderate certainty), however, was not linked to a significantly lower risk for death in comparison with standard oxygen.

Compared with high-flow nasal oxygen (RR, 0.46; absolute risk difference, –0.15; low certainty) and face mask NIV (RR, 0.48; absolute risk difference, –0.13; low certainty), helmet NIV was associated with significantly decreased mortality.

"In the case of face mask, we saw a very small marginal benefit in mortality, and that is a little bit against most recent trials, like the Frat trial," Ferreyro said. "That association did not stand in multiple scenarios, for example, in patients with more severe respiratory states."

The risk for endotracheal intubation was lower among those who received helmet NIV (RR, 0.26; absolute risk difference, –0.32; low certainty), face mask NIV (RR, 0.76; absolute risk difference, –0.12; moderate certainty), and high-flow nasal oxygen (RR, 0.76; absolute risk difference, –0.11; moderate certainty) (25 studies; 3804 patients) in comparison with standard oxygen.

The risk for bias resulting from lack of blinding for intubation was determined to be high.

Helmet NIV was linked to reduced risk for endotracheal intubation compared with high-flow nasal oxygen (RR, 0.35; absolute risk difference, −0.20; low certainty) and face mask NIV (RR,0.35; absolute risk difference, −0.20; low certainty).

There was no significant difference in the risk for endotracheal intubation with face mask NIV vs high-flow nasal oxygen (RR, 1.01; absolute risk difference, −0.00; low certainty).

Regarding concerns that these technologies could harm patients, "There is all upside and no downside" to using them, Lisa F. Wolfe, MD, associate professor of medicine (pulmonary and critical care), Northwestern University, Chicago, Illinois, told *Medscape Medical News*.

"There have been concerns that if we use this advanced technology, it might in some way harm patients by slowing down their access to intubation and mechanical ventilation," but the meta-analysis shows the technology does not harm patients, she added.

Which Patients Benefit Remains Unclear

"Questions remain for clinicians regarding when and for which patients these various noninvasive oxygen support strategies fit into the algorithm of AHRF management and specifically for patients with COVID-19," Bhakti K. Patel, MD, Section of Pulmonary and Critical Care Medicine, Pritzker School of Medicine, University of Chicago, Illinois, and colleagues write in an accompanying editorial.

"Although some have argued that the risk of spontaneous breathing should preclude any noninvasive oxygen support, the data from the analysis by Ferreyro et al indicate that it is a reasonable approach to spare a subset of patients with AHRF invasive mechanical ventilation and its inherent complications," Patel and colleagues continue.

The included studies make it difficult to determine which individual patients might benefit the most from NIV, Wolfe said. The most common diagnoses of the included patients were pneumonia and chronic obstructive pulmonary disease, she explained. She noted that there is a need for additional research to explore these questions.

"Given this is a network meta-analysis of aggregated data, we could not explore in detail which individual patient factors make them more likely to respond to any of these interventions," Ferreyro said. "There's still a struggle to identify which specific patients will likely benefit from each of these strategies," he added.

Patel and colleagues caution against using a "one-size-fits-all" approach to NIV. They recommend "a precision-based approach that matches a given strategy to the observed phenotype of AHRF coupled with incorporating clinician experience and comfort with each technology.

"Although further studies are needed, the meta-analysis by Ferreyro et al has provided a useful summary of the available data to help inform clinicians as they determine locally the best way to choose wisely among several options for care of patients with AHRF, especially in the wave of patients with COVID-19 currently being encountered. Future clinical trials comparing these strategies should not focus on declaring a 'winner' per se but rather on identifying the patient phenotypes that stand to benefit from each noninvasive oxygenation support method. In the management of heterogeneous syndromes like AHRF, it is better to have multiple options than to focus on limiting clinical practice to a single choice," Patel and colleagues write.

Patients with interstitial lung disease and other conditions also experience hypoxemia, Wolfe said, adding, "The 'next evolution' of this is going to be expanding access to these types of support devices in the outpatient arena because hypoxemia is seen in COPD in outpatients" as well as inpatients.

Study coauthor Ferguson has received personal fees from Xenios and Getinge. The other coauthors have disclosed no relevant financial relationships. Editorialist Patel has received grants from the Parker B. Francis Foundation outside the submitted work. The remaining coauthors have disclosed no relevant financial relationships. Wolfe has disclosed no relevant financial relationships.

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https://bit.ly/2UHXCBo

Sugar coating locks and loads coronavirus for infection

The coronavirus uses a sugary coating of molecules called glycans to camouflage itself as harmless from the defending antibodies

by Jorge Salazar, Texas Advanced Computing Center

They say you can't judge a book by its cover. But the human immune system does just that when it comes to finding and attacking harmful microbes such as the coronavirus. It relies on being able to recognize foreign intruders and generate antibodies to destroy them. Unfortunately, the coronavirus uses a sugary coating of molecules called glycans to camouflage itself as harmless from the defending antibodies.

Simulations on the National Science Foundation (NSF)-funded Frontera supercomputer at the Texas Advanced Computing Center (TACC) have revealed the atomic makeup of the coronavirus's sugary shield. What's more, simulation and modeling show that glycans also prime the coronavirus for infection by changing the shape of its spike protein. Scientists hope this basic research will add to the arsenal of knowledge needed to defeat the COVID-19 virus.

Sugar-like molecules called glycans coat each of the 65-odd spike proteins that adorn the coronavirus. Glycans account for about 40 percent of the spike protein by weight. The spike proteins are

critical to cell infection because they lock onto the cell surface, giving the virus entry into the cell.

"You really see how effective its glycan shield is," said Rommie Amaro, a professor of chemistry and biochemistry at the University of California, San Diego. "That's because you see the glycans covering the surface of the viral spike protein, which is the most exposed bit and the part that's responsible for the initial infection in the human cell," she said.

Amaro is a corresponding author of a study published June 12, 2020 on bioRxiv.org—an open-access repository of electronic preprints—that discovered a potential structural role of the shielding glycans that cover the SARS-CoV-2 spike protein. "You can see very clearly that from the open conformation, the spike protein has to undergo a large structural change to actually get into the human cell," Amaro said.

But even to make an initial connection, she said that one of the pieces of the spike protein in its receptor binding domain has to lift up. "When that receptor binding domain lifts up into the open conformation, it actually lifts the important bits of the protein up over the glycan shield," Amaro explained.

This is in contrast to the closed conformation, where the shield covers the spike protein. "Our analysis gives a potential reason why it does have to undergo these conformational changes, because if it just stays in the down position those glycans are basically going to block the binding from actually happening," she said.

Another aspect of their study showed how shifts in the conformations of the glycans triggered changes in the spike protein structure. "One thing that really jumped out at us is that in the open conformation there are two glycans that basically prop up the protein in that open conformation," Amaro said.

"That was really surprising to see. It's one of the major results of our study. It suggests that the role of glycans in this case is going beyond shielding to potentially having these chemical groups actually being involved in the dynamics of the spike protein," she added.

She likened the action of the glycan to pulling the trigger of a gun. "When that bit of the spike goes up, the finger is on the trigger of the infection machinery. That's when it's in its most dangerous mode—it is locked and loaded," Amaro said. "When it gets like that, all it has to do is come up against an ACE2 receptor in the human cell, and then it's going to bind super tightly and the cell is basically infected."

The NSF-funded Frontera supercomputer of the Texas Advanced Computing Center at UT Austin is ranked #5 fastest in the world and #1 for academic systems, according to the November 2019 Top500 rankings. Credit: TACC

Amaro and her colleagues use computational methods to build data-centric models of the SARS-CoV-2 virus, and then use computer simulations to explore different scientific questions about the virus.

They started with various experimental datasets that revealed the structure of the virus. This included cryo-EM structures from the Jason McLellan Lab of The University of Texas at Austin; and from the lab of David Veesler at the University of Washington. "Their structures are really amazing because they give researchers a picture of what these important molecular machines actually look like," Amaro said.

Unfortunately, even the most powerful microscopes on Earth still can't resolve movement of the protein at the atomic scale. "What we do with computers is that we take the beautiful and wonderful and important data that they give us, but then we use methods to build in missing bits of information," Amaro said.

What's more, details of the glycan shielding have been too difficult for experiments to resolve. "What people really want to know, for

example vaccine developers and drug developers, is what are the vulnerabilities that are present in this shield," Amaro said.

The computer simulations allowed Amaro and colleagues to create a cohesive picture of the spike protein that includes the glycans. "The reason why the computer resources at TACC are so important is that we can't understand what these glycans look like if we don't use simulation," Amaro said.

Amaro was awarded compute time on the NSF-funded Frontera supercomputer of TACC. Her team has used about 2.3 million node hours for molecular dynamics simulations and modeling , the most among any researchers using the system to study COVID-19. She used up to 4,000 nodes, or about 250,000 processing cores. Frontera—the leadership-class system in NSF's cyberinfrastructure ecosystem—ranks as the fifth most powerful supercomputer in the world and the fastest academic system, according to November 2019 rankings of the Top500 organization.

In order to animate the dynamics of the 1.7 million atom system under study, a lot of computing power was needed, said Amaro. "That's really where Frontera has been fantastic, because we need to sample relatively long dynamics, microsecond to millisecond timescales, to understand how this protein is actually working."

"We've been able to do that with Frontera and the COVID-19 HPC Consortium," Amaro said. "Now we're trying to share our data with as many people as we can, because people want a dynamical understanding of what's happening—not only with other academic groups but also with different pharmaceutical and biotech companies that are conducting neutralizing antibody development," she said.

Basic research is making a difference in winning the war against the SARS-CoV-2 virus, Amaro explained. "The more we know about it, the more of its abilities that we're going to be able to go after and potentially take out," she added.

Said Amaro: "It's of such great importance that we learn as much as we can about the virus. And then hopefully we can translate those understandings into things that will be useful either in the clinic, or the streets, for example if we're trying to reduce transmission for what we know now about aerosols and wearing masks. All these things will be part of it. Basic research has a huge role to play in the war against COVID-19. And I'm happy to be a part of it. It's a strength that we have Frontera and TACC in our arsenal."

The study, "Shielding and Beyond: The Roles of Glycans in SARS-CoV-2 Spike Protein," was published on bioRxiv.org June 12, 2020. The study authors are Lorenzo Casalino, Zied Gaieb, Abigail C. Dommer, Rommie E. Amaro of the Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA; and Aoife M Harbison, Carl A Fogarty, Elisa Fadda of the Department of Chemistry and Hamilton Institute, Maynooth University, Dublin, Ireland. This work was supported by NIH GM132826, NSF RAPID MCB-2032054, an award from the RCSA Research Corp., a UC San Diego Moore's Cancer Center 2020 SARS-COV-2 seed grant, the Visible Molecular Cell Consortium, and the Irish Research Council.

More information: *Lorenzo Casalino et al. Shielding and Beyond: The Roles of Glycans in SARS-CoV-2 Spike Protein, bioRxiv (2020). DOI: 10.1101/2020.06.11.146522*