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Activating an estrogen receptor can stop pancreatic cancer cells from growing

Penn study shows GPER activation in mice can also make tumors more visible to immune system

PHILADELPHIA - Activating the G protein-coupled estrogen receptor (GPER) - a receptor found on the surface of many normal and cancer tissues - has been shown to stop pancreatic cancer from growing, but may also make tumors more visible to the immune system and thus more susceptible to modern immunotherapy. Researchers at the Perelman School of Medicine at the University of Pennsylvania and Penn's Abramson Cancer Center observed the effects of GPER activation in human and mouse pancreatic cancer models and published their findings in *Cellular and Molecular Gastroenterology and Hepatology* today.

For most cancer types, including pancreas, women generally have better outcomes than men. Although the reasons for this are only now emerging, researchers have known for decades that there is a link between the body's sex hormones and some types of cancer, especially those arising in reproductive tissues such as breast and prostate. However, the idea that cancers in non-reproductive tissues might also be influenced by sex steroid hormones has only recently been considered.

Building on their research showing the anti-cancer activity of GPER in melanoma models, Todd W. Ridky, MD, PhD, an assistant professor of Dermatology at Penn and the study's senior author, and his lab, examined whether GPER activators may also inhibit other cancer types.

"We know that activating GPER in melanoma models stops the growth of cancer cells and make the tumors themselves more immunogenic, so we wanted to find out what would happen if we selectively activated GPER other tumor types. In this study we examined several pancreatic cancer models and found that synthetic small molecule GPER activators potently inhibited pancreatic cancer cells, and simultaneously rendered the tumor cells more sensitive to other anti-cancer therapies," Ridky said.

For this study, the Ridky lab worked with the Penn Pancreatic Cancer Research Center (PCRC), directed by study co-author Ben Z. Stanger, MD, PhD, the Hanna Wise Professor in Cancer Research. Using new PCRC mouse pancreatic cancer models, the multidisciplinary team was able to show GPER's impact on pancreatic cancer growth. In some models, GPER activation inhibited growth and made tumors more sensitive to anti-PD-1 immunotherapy, pointing to the translational potential of improving the efficacy of existing treatments in a cancer type where PD-1 inhibitors have not historically been very effective.

The use of GPER activators is a novel idea in cancer therapy, and has a key difference from most anti-cancer agents. Nearly all current cancer drugs act to block the activity of cellular proteins that are needed by not only the cancer cells, but also by normal cells. As a result, most cancer drugs are associated with major toxicity. In contrast, the estrogenic analog used in the Penn study activates GPER. This approach mirrors something that naturally occurs in the body, as GPER is already present and normally activated by estrogen, especially in females during pregnancy.

"Likely because this is something the human body is already accustomed to, evidence from preclinical animal studies suggested that side effects to this approach would likely be minimal when this moves into the clinic," said the study's first author Christopher Natale, Ph.D., Ridky's former graduate student.

Natale is currently the Vice President of Research at Linnaeus Therapeutics, a company he and Ridky co-founded to further investigate the translational potential of this work. A multi-site Phase I trial in patients with advanced cancer is currently ongoing.

Additional Penn authors on the study include Jinyang Li, Jason R. Pitarresi, Robert J. Norgard, Tzvete Dentchev, Brian C. Capell, and John T. Seykora.
The study was supported by the National Institutes of Health (R01 CA163566, P50CA174523, T32 AR0007465 - 32, F31 CA206325, R41CA228695), the Melanoma Research Foundation, the Dermatology Foundation, and the Penn Skin Biology and Diseases Resource-based Center (P30 - AR069589).
Editor's Note: Ridky and Natale are scientific co-founders of Linnaeus Therapeutics and hold equity in the company. They are inventors on intellectual property related to this work and may receive additional financial benefits in the future. Penn is also an investor in the company, holds equity interests, and has licensed intellectual property to the company related to this work.

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Billions projected to suffer nearly unlivable heat in 2070

A new study released Monday, May 4, 2020, says 2 to 3.5 billion people in 50 years will be living in a climate that historically has proven just too hot to handle.

by Seth Borenstein

Currently about 20 million people live in places with an annual average temperature greater than 84 degrees (29 degrees Celsius)—far beyond the temperature sweet spot. That area is less than 1% of the Earth's land, and it is mostly near the Sahara Desert and includes Mecca, Saudi Arabia. (AP Photo/Mosa'ab Elshamy, File)

In just 50 years, 2 billion to 3.5 billion people, mostly the poor who can't afford air conditioning, will be living in a climate that historically has been too hot to handle, a new study said.

With every 1.8 degree increase in global average annual temperature from man-made climate change, about a billion or so people will end up in areas too warm day-in, day-out to be habitable without cooling technology, according to ecologist Marten Scheffer of Wageningen University in the Netherlands, co-author of the study.

How many people will end up at risk depends on how much heat-trapping carbon dioxide emissions are reduced and how fast the world population grows. Under the worst-case scenarios for population growth and for carbon pollution—which many climate scientists say is looking less likely these days—the study in Monday's journal *Proceedings of the National Academy of Sciences* predicts about 3.5 billion people will live in extremely hot areas. That's a third of the projected 2070 population.

But even scenarios considered more likely and less severe project that in 50 years a couple of billion people will be living in places too hot without air conditioning, the study said.

"It's a huge amount and it's a short-time. This is why we're worried," said Cornell University climate scientist Natalie Mahowald, who wasn't part of the study. She and other outside scientists said the new study makes sense and conveys the urgency of the man-made climate change differently than past research.

In an unusual way to look at climate change, a team of international scientists studied humans like they do bears, birds and bees to find the "climate niche" where people and civilizations flourish. They looked back 6,000 years to come up with a sweet spot of temperatures for humanity: Average annual temperatures between 52 and 59 degrees.

We can—and do—live in warmer and colder places than that, but the farther from the sweet spot, the harder it gets.

A new study released Monday, May 4, 2020, says 2 to 3.5 billion people in 50 years will be living in a climate that historically has proven just too hot to handle. Currently about 20 million people live in places with an annual average temperature greater than 84 degrees (29 degrees Celsius)—far beyond the temperature sweet spot. That area is less than 1% of the Earth's land, and it is mostly near the Sahara Desert and includes Mecca, Saudi Arabia. (AP Photo/Mosa'ab Elshamy, File)

The scientists looked at places projected to get uncomfortably and considerably hotter than the sweet spot and calculated at least 2 billion people will be living in those conditions by 2070.

Currently about 20 million people live in places with an annual average temperature greater than 84 degrees (29 degrees Celsius) – far beyond the temperature sweet spot. That area is less than 1% of the Earth's land, and it is mostly near the Sahara Desert and includes Mecca, Saudi Arabia.

But as the world gets more crowded and warmer, the study concluded large swaths of Africa, Asia, South America and Australia will likely be in this same temperature range. Well over 1 billion people, and up to 3.5 billion people, will be affected depending on the climate altering choices humanity makes over the next half century, according to lead author Chi Xu of Nanjing University in China.

With enough money, "you can actually live on the moon," Scheffer said. But these projections are "unlivable for the ordinary, for poor people, for the average world citizen."

Places like impoverished Nigeria—with a population expected to triple by the end of he century—would be less able to cope, said study co-author Tim Lenton, a climate scientist and director of the Global Systems Institute at the University of Exeter in England.

More information: *Chi Xu el al., "Future of the human climate niche," PNAS (2020). www.pnas.org/cgi/doi/10.1073/pnas.1910114117*

https://bit.ly/2WaGncK

New Paper Has a Wild Explanation For The Most Explosive 'Meteor Impact' on Record

Iron asteroid entering Earth's atmosphere and skimming the planet at a relatively low altitude before flying back into space

Michelle Starr

In the early morning of 30 June 1908, something exploded over Siberia. The event shattered the normal stillness of the sparsely populated taiga, so powerful that it flattened an area of forest 2,150 square kilometres (830 square miles) in size - felling an estimated 80 million trees.

Eyewitness reports describe a brilliant ball of light, shattered windows and falling plaster, and a deafening detonation not far from the local river. The Tunguska event - as it came to be known - was later characterised as an exploding meteor, or bolide, up to 30 megatons, at an altitude of 10 to 15 kilometres (6.2 to 9.3 miles).

It is often referred to as the "largest impact event in recorded history", even though no impact crater was found. Later searches have turned up fragments of rock that could be meteoric in origin, but the event still has a looming question mark. Was it really a bolide? And if it wasn't, what could it be?

Well, it's possible we'll never actually know… but according to a recent peer-reviewed paper, a large iron asteroid entering Earth's atmosphere and skimming the planet at a relatively low altitude before *flying back into space* could have produced the effects of the Tunguska event by producing a shock wave that devastated the surface.

"We have studied the conditions of through passage of asteroids with diameters 200, 100, and 50 metres, consisting of three types of materials - iron, stone, and water ice, across the Earth's atmosphere with a minimum trajectory altitude in the range 10 to 15 kilometres," wrote researchers led by astronomer Daniil Khrennikov of the Siberian Federal University in their paper.

"The results obtained support our idea explaining one of the long-standing problems of astronomy - the Tunguska phenomenon, which has not received reasonable and comprehensive interpretations to date. We argue that the Tunguska event was caused by an iron asteroid body, which passed through the Earth's atmosphere and continued to the near-solar orbit."

The team mathematically modelled the passage of all three asteroid compositions at different sizes to determine whether such an event is possible.

The ice body - a hypothesis floated by Russian researchers in the 1970s - was pretty simple to rule out. The heat generated by the speed required to obtain the estimated trajectory would have entirely melted the ice body before it reached the distance observational data suggests it covered.

The rocky body, too, would be less likely to survive. Meteors are thought to explode when air enters the body through small fractures in the meteor, causing a build-up of pressure as it flies through the air at high speed. Iron bodies are much more resistant to fragmentation than rocky ones.

According to the team's calculations, the most likely culprit is an iron meteorite between 100 and 200 metres (320 to 650 feet) across that flew 3,000 kilometres (1,800 miles) through the atmosphere. It would never have dropped below 11.2 kilometres per second (7 mps), or below an altitude of 11 kilometres.

This model would explain several characteristics of the Tunguska event. The lack of an impact crater, for one, since the meteor would skim past the epicentre of the explosion without falling.

The lack of iron debris is also explained by this high velocity, since the object would be moving too fast, and would be too hot, to drop much. Any mass lost would be, the researchers said, through the sublimation of individual iron atoms, which would look exactly like normal terrestrial oxides.

"Within this version," the researchers also noted, "we can explain optical effects associated with a strong dustiness of high layers of the atmosphere over Europe, which caused a bright glow of the night sky."

While the results are certainly compelling, the researchers note their paper has some limitations they hope can be resolved with future research. For one, they "did not deal with the problem of the formation of a shockwave", although their initial comparisons to the Chelyabinsk meteorite allow for a huge shockwave to have plausibly occurred in Tunguska.

Nevertheless, the idea of an iron body pummelling through our atmosphere certainly is intriguing, and we can look forward to more papers on the subject. The research has been published in the *Monthly Notices of the Royal Astronomical Society*.

https://bit.ly/35C8sqq

New evidence that higher caffeine and urate levels are protective against Parkinson's

Analysis of participants in the Harvard biomarkers study highlights the inverse association between low caffeine consumption

Amsterdam, NL - Two purines, caffeine and urate, have been associated with a reduced risk of Parkinson's disease (PD) in multiple study groups and populations. Analysis of data from the Harvard Biomarkers Study shows that lower levels of caffeine consumption and lower blood urate are inversely associated with PD, strengthening the links between caffeine intake and urate levels and PD, reports a study in the *Journal of Parkinson's Disease (JPD).*

"Both caffeine and urate possess neuroprotective properties via adenosine receptor antagonist and antioxidant actions, respectively," explained lead investigator Rachit Bakshi, PhD, Department of Neurology, Massachusetts General Hospital, and Harvard Medical School, Boston, MA. "They both have protective properties in animal models of PD, raising the possibility of their disease-slowing potential."

Researchers therefore investigated whether these reduced risk factors are associated with PD in participants in the Harvard Biomarkers Study (HBS), which is a longitudinal study designed to

accelerate the discovery and validation of molecular diagnostic and progression markers of early-stage PD.

Investigators conducted a cross-sectional, case-control study of 369 individuals with idiopathic PD and 197 healthy controls from the full HBS cohort. Urate was measured in plasma samples collected at each participant's initial HBS visit. Caffeine intake was also assessed at each participant's initial HBS visit using a semi-quantitative questionnaire. The questionnaire queried participants' usual consumption of caffeinated and decaffeinated coffee, tea, and soft drinks during the previous 12 months in standard volumes (cups for coffee and tea and cans for soft drinks) with nine possible frequencies ranging from never to six or more per day.

Caffeine intake was lower in idiopathic PD patients compared to healthy controls. The odds of having PD decreased significantly with increasing caffeine consumption in a concentration-dependent manner across quintiles of caffeine consumption, adjusting for age, sex, BMI, and plasma urate. Compared with the lowest caffeine consumption quintile, the prevalence of PD was over 70 percent lower in the highest quintile. A strong inverse association was also observed with plasma urate levels both in males and females. An equally large association between urate and PD risk was observed among women, in contrasts with most prior studies of the association between urate and idiopathic PD stratified by sex. These findings support the generalizability of discoveries made with this cohort, which is well suited for deep analysis of relationships between dietary factors, genes, established and novel biomarkers, and clinical phenotypes of PD.

"The strength of this new study relates to the robust approach, including the large and carefully followed cohort of people living with PD and the comprehensive set of outcome measures. It is an important basis to further develop future disease-modifying approaches to slow down the decline of this otherwise relentlessly progressive condition," added Prof. Bas Bloem, Co-Editor-in-Chief of the journal.

The investigators caution that a recent large clinical trial of a urate-elevating treatment failed to demonstrate a benefit for people with PD over months to years. Thus, even though the current study strengthens the link between PD and lower urate levels, strategies to raise them may be harmful and cannot be recommended. Caffeine has yet to be rigorously studied in a long-term PD trial, therefore increasing one's caffeine intake cannot be recommended. Nevertheless, people who currently enjoy caffeine in coffee or tea may take additional pleasure in knowing of its therapeutic even if unproven potential, they point out.

"Identifying factors that are linked to lower likelihood of PD, such as caffeine consumption, offer a unique opportunity to understand the disease, and if the link were causal, then possibly to slow the disease," concluded Dr. Bakshi.

PD is a slowly progressive disorder that affects movement, muscle control and balance. It is the second most common age-related neurodegenerative disorder affecting about 3% of the population by the age of 65 and up to 5% of individuals over 85 years of age.

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A Microbe That Seems to Stop Mosquitoes Spreading Malaria Has Been Found

Although COVID-19 is dominating headlines, other diseases don't let up just because we have a pandemic - and malaria is still as dangerous as ever.

Jacinta Bowler

In 2018, the World Health Organisation estimated 228 million cases of the mosquito-borne disease, and 405,000 deaths.

But a new study may have found a brand new, highly effective way to stop the spread – and it was inside the mosquito all along.

The team discovered that a new type of spore-forming single-celled microbe found in mosquitoes, which they've called *Microsporidia MB*, has the amazing ability to stop the transmission of *Plasmodium falciparum* – the parasitic protozoan which causes most malaria cases.

It also doesn't seem to hurt the mosquito, meaning that if we can increase the prevalence of *Microsporidia MB* in local mosquito populations, it could be a good way to stop malaria in its tracks without having to mess up the rest of the ecosystem.

"Here, we characterise an apparently non-pathogenic microsporidian from field populations of *Anopheles arabiensis* [a species of mosquito] in Kenya," the team writes in a new paper.

"As a microbe that impairs *Plasmodium* transmission that is non-virulent and vertically transmitted, *Microsporidia MB* could be investigated as a strategy to limit malaria transmission."

The idea that a mosquito microbe could be stopping the transmission of a disease isn't exactly new. *Wolbachia*, a genus of bacteria that naturally occurs in mosquito populations, has shown incredible potential for wiping out dengue and other mosquito-borne infections.

"We are already using a transmission-blocking symbiont called *Wolbachia* to control dengue, a virus transmitted by mosquitoes," University of Glasgow microbiologist Steven Sinkins says.

"The *Microsporidia MB* symbiont has some similar characteristics, making it an attractive prospect for developing comparable approaches for malaria control."

This research is currently in its early stages – but the team found that when they analysed mosquitoes taken from field studies in Kenya, those with *Microsporidia MB* did not have the malaria parasite. Even when they let the mosquitoes drink infected blood, the mosquitoes with *Microsporidia MB* had reduced levels of infection and no signs of the malaria parasite's spores were detected.

Because *Microsporidia MB* is passed down the maternal line, once it's in the mosquito population, it's unlikely to be going anywhere. The team found that some areas they tested already had nine percent of the mosquito population with the malaria-busting microbe.

The team hopes that with more research we can find out if it's possible to increase the amount of *Microsporidia MB* in the mosquito population – with the eventual goal of lowering rates of malaria.

"Further studies will be needed to determine precisely how *Microsporidia MB* could be used to control malaria. The next phase of the research will investigate *Microsporidia MB* dynamics in large mosquito populations in screen house 'semi-field' facilities," says International Centre of Insect Physiology and Ecology microbiologist, Jeremy Herren.

"The results of these studies will give us key information that will be used to determine how we could then disseminate *Microsporidia MB* for malaria control."

The research has been published in *Nature Communications*.

https://bit.ly/3bb9Pnl

Ancient 'Tully monster' was a vertebrate, not a spineless blob, study claims

An odd carboniferous creature with eyes like a hammerhead was this: a vertebrate.

By Laura Geggel - Associate Editor

There are few ancient creatures as controversial as the Tully monster, a bowling-pin-sized oddity with eyes like a hammerhead that lived about 307 million years ago. Now, after decades of studies, each with a different take on how to define the weird aquatic creature, the Tully monster has been decoded: It's a vertebrate, meaning it had a backbone, a new study finds.

Scientists analyzed the chemical residues left on fossilized remains of the Tully monster (*Tullimonstrum gregarium*) and compared them with the chemical remnants on other vertebrate and invertebrate fossils from the monster's ancient home in what is now Mazon Creek in northeastern Illinois, said study lead researcher Victoria McCoy, a visiting assistant professor of geosciences at the University of Wisconsin-Milwaukee.

An illustration of the Tully monster, a weird creature with hammerhead-like eyes and a slender snout. **© Shutterstock**

McCoy and her colleagues took a "chemical approach" rather than looking at the Tully monster's fossilized anatomy, which is "kind of like a Rorschach test," McCoy told Live Science. Ever since amateur fossil collector Francis Tully discovered the monster's remains in 1958, researchers looking at the anatomy have interpreted the beast to be all kinds of things, including a vertebrate, an invertebrate, a shell-less snail, a type of worm, a jawless fish and an arthropod, or a member of a group that includes insects, spiders and lobsters.

"Due to all the back and forth, we thought that maybe just investigating the [anatomy] would never be enough to end the debate," McCoy said. "We decided then to go look at the chemistry of the Tully monster fossils to understand what the different tissues were made of."

To determine whether the Tully monster was a vertebrate or invertebrate, the team decided to see if its fossils held the remnants of chitin, a long string of sugar molecules which makes up the "harder, crunchier tissues" in the exoskeletons and teeth of invertebrates, or the remnants of proteins that make up the keratin and collagen found in vertebrates, McCoy said.

The scientists used "in situ Raman microspectroscopy," which is a nondestructive method (meaning it doesn't harm the fossil) that involves shooting a laser at the specimen. The laser's energy causes the different chemical bonds within the specimen to vibrate, each at their own unique rate. By graphing these rates, scientists can determine what kinds of compounds are present.

"It's extremely difficult to identify one compound," McCoy said. "But, as long as you know what classes of compounds make up those in your sample, that's enough to distinguish vertebrates from invertebrates."

The team looked at 32 different spots on 20 fossils, including three Tully monster specimens and 17 other ancient animals. The results revealed that Tully had a backbone, she said.

"The Tully monsters, all of its tissues that we analyzed, were made up of proteins and none of them were made up of chitin," McCoy said. "So, that is really strong evidence that the Tully monster was, in fact, a vertebrate."

The Tully monster was about 1 foot (0.3 meters) long. **Sean McMahon/Yale University**

This finding jibes with a 2016 study in the journal Nature by the same team, which suggested that the Tully monster was a jawless fish in the same lineage as the modern-day lamprey.

However, this study isn't the final word on the Tully monster's true identity, two researchers who were not involved with the new study told Live Science.

For instance, the interpretation of Raman spectra of complex geological material "is not straightforward. This is why the authors use statistical methods to tease apart the differences in Raman spectra," Shuhai Xiao, a professor of geobiology at Virginia Tech, told Live Science in an email.

However, Xiao added that gathering and analyzing Raman spectroscopy data "can potentially provide new insights into the study of problematic fossils, such as Tully monster."

It would have been helpful if the analysis had included more specimens, both of Tully monsters and other equally ancient animals from Mazon Creek, Steven Jasinski, the paleontologist at the State Museum of Pennsylvania, told Live Science. However, "their results are good and I think it definitely is suggestive that Tully monster is a vertebrate. I just don't think it's the endpoint."

"I think more study will have to go in to confer or refute their results," said Jasinski, who was not involved in the current study. "But I definitely think it's a step toward seeing the Tully monster might be a really weird, abnormal vertebrate."

The study was published online April 28 in the journal Geobiology.

https://bit.ly/3bqltNM

Astronomers find Jupiter-like cloud bands on closest brown dwarf

Closest known brown dwarf, Luhman 16A, shows signs of cloud bands similar to those seen on Jupiter and Saturn.

A team of astronomers has discovered that the closest known brown dwarf, Luhman 16A, shows signs of cloud bands similar to those seen on Jupiter and Saturn. This is the first time scientists have used the technique of polarimetry to determine the properties of atmospheric clouds outside of the solar system, or exoclouds.

Brown dwarfs are objects heavier than planets but lighter than stars, and typically have 13 to 80 times the mass of Jupiter. Luhman 16A is part of a binary system containing a second brown dwarf, Luhman 16B. At a distance of 6.5 light-years, it's the third closest system to our Sun after Alpha Centauri and Barnard's Star. Both brown dwarfs weigh about 30 times as much as Jupiter.

Despite the fact that Luhman 16A and 16B have similar masses and temperatures (about 1,900° F or 1,000° C), and presumably formed at the same time, they show markedly different weather. Luhman 16B shows no sign of stationary cloud bands, instead exhibiting evidence of more irregular, patchy clouds. Luhman 16B therefore has noticeable brightness variations as a result of its cloudy features, unlike Luhman 16A.

"Like Earth and Venus, these objects are twins with very different weather," said Julien Girard of the Space Telescope Science Institute in Baltimore, Maryland, a member of the discovery team. "It can rain things like silicates or ammonia. It's pretty awful weather, actually."

The researchers used an instrument on the Very Large Telescope in Chile to study polarized light from the Luhman 16 system. Polarization is a property of light that represents the direction that the light wave oscillates. Polarized sunglasses block out one direction of polarization to reduce glare and improve contrast.

"Instead of trying to block out that glare, we're trying to measure it," explained lead author Max Millar-Blanchaer of the California Institute of Technology (Caltech) in Pasadena, California.

When light is reflected off of particles, such as cloud droplets, it can favor a certain angle of polarization. By measuring the preferred polarization of light from a distant system, astronomers can deduce the presence of clouds without directly resolving either brown dwarf's cloud structure.

"Even from light-years away, we can use polarization to determine what the light encountered along its path," added Girard.

"To determine what the light encountered on its way we compared observations against models with different properties: brown dwarf atmospheres with solid cloud decks, striped cloud bands, and even brown dwarfs that are oblate due to their fast rotation. We found that only models of atmospheres with cloud bands could match our

observations of Luhman 16A," explained Theodora Karalidi of the University of Central Florida in Orlando, Florida, a member of the discovery team.

The polarimetry technique isn't limited to brown dwarfs. It can also be applied to exoplanets orbiting distant stars. The atmospheres of hot, gas giant exoplanets are similar to those of brown dwarfs. Although measuring a polarization signal from exoplanets will be more challenging, due to their relative faintness and proximity to their star, the information gained from brown dwarfs can potentially inform those future studies.

NASA's upcoming James Webb Space Telescope would be able to study systems like Luhman 16 to look for signs of brightness variations in infrared light that are indicative of cloud features. NASA's Wide Field Infrared Survey Telescope (WFIRST) will be equipped with a coronagraph instrument that can conduct polarimetry, and may be able to detect giant exoplanets in reflected light and eventual signs of clouds in their atmospheres.

This study has been accepted for publication in The *Astrophysical Journal*.

More information: *Maxwell A. Millar-Blanchaer et al. Detection of Polarization due to Cloud Bands in the Nearby Luhman 16 Brown Dwarf Binary, The Astrophysical Journal (2020). DOI: 10.3847/1538-4357/ab6ef2*

https://bit.ly/35Fn52l

Researchers unlock TB vaccine puzzle in findings that could save millions of newborns

What makes the 100-year-old TB vaccine so effective at preventing newborn deaths from other diseases?

An international research team has identified the mechanism behind one of science's most enduring mysteries: what makes the 100-year-old tuberculosis (TB) vaccine so effective at preventing newborn deaths from diseases other than TB?

The ability of Bacillus Calmette-Guérin (BCG)--one of the oldest, safest and cheapest vaccines available--to provide protection to newborns beyond its intended purpose of fighting off TB has been known since at least the 1940s, but until now no one has been able to explain why or show how it works.

In a new study, published today in *Science Translational Medicine*, researchers reveal how they identified a dramatic and rapid increase in neutrophils -- white blood cells that patrol the body and destroy invading bacterial pathogens - in mice and babies within three days of BCG vaccination.

The five-year study is the first to demonstrate the beneficial mechanism triggered by administration of BCG in newborns. It involved researchers from around the world, including senior co-authors Dr. Tobias Kollmann, an affiliate professor in the UBC department of paediatrics, and Dr. Nelly Amenyogbe, a graduate of UBC's experimental medicine program. The study's lead author Byron Brook, a UBC PhD candidate in experimental medicine, is based at the Kollmann Lab at BC Children's Hospital Research Institute in Vancouver.

"It's been known for a very long time that neutrophils play a very important role in managing sepsis, but until now nobody understood the role of BCG in initiating this critical process," said Amenyogbe. "It was actually thought to be biologically implausible, however we've not only shown how BCG is involved, but that it kicks off this process almost instantly following vaccination -- far more quickly than anticipated."

The researchers first witnessed the phenomenon--known as emergency granulopoiesis (EG)--in mice, with the team later validating it in blood samples from newborn babies in West Africa and Papua New Guinea.

Kollmann, who also heads up the Systems Vaccinology team at Telethon Kids Institute (TKI) in Australia in partnership with the

Perth Children's Hospital Foundation, said the findings reinforce how critical it is for newborns in low-resource settings to receive BCG immediately after birth. Kollmann was previously the head of the paediatric division of infectious diseases at UBC before relocating to Australia.

"Less than half the babies who should get this vaccine right after birth actually get it then, partly because of logistics and partly because TB is not seen as a huge risk in those first few weeks. Administration is often delayed to four to six weeks, but by then it's too late for many newborns," said Kollmann, also an affiliate investigator at BC Children's Hospital in Vancouver. "Around half of all newborn deaths from infection happen in the first week of life, with about 75 per cent of those deaths caused by sepsis. Given BCG's clear role in helping newborns to fight off sepsis, we could save the lives of close to a million newborns every year if they were given this vaccine within days of birth instead of weeks later."

Brook, the study's lead author, added: "If every newborn was vaccinated with BCG, the greatest impact would be in regions of highest newborn mortality, specifically low- and middle-income countries. It could also help save newborns here in Canada, and represents a new strategy of how to get more benefit from existing vaccines."

The researchers cautioned that while the effect was rapid and offered robust protection against newborn sepsis, it was relatively short-lived and did not occur in adult mice.

Kollmann and Amenyogbe are also involved in Australia's BRACE trial, which is testing BCG's potential to fight off COVID-19. Kollmann said whether BCG may or may not be protective against COVID-19 remains to be seen, but in the meantime, its real and proven potential to save the lives of vulnerable newborns had to be maximized.

"BCG is very, very safe, costs only a few cents per dose, and reduces infectious causes of mortality - not just tuberculosis - in newborns by almost 50 per cent," Kollmann said. "There's nothing that we have in our entire current medical arsenal that is as effective, cheap, safe, feasible and affordable as this vaccine. All we have to do is ensure all newborns at risk get it right away at birth."

https://go.nature.com/2L570tz

China is promoting coronavirus treatments based on unproven traditional medicines

Scientists say rigorous trial data are needed to show that remedies are safe and effective.

David Cyranoski

The Chinese government is heavily promoting traditional medicines as treatments for COVID-19. The remedies, a major part of China's health-care system, are even being sent to countries including Iran and Italy as international aid. But scientists outside China say it is dangerous to support therapies that have yet to be proved safe and effective.

Traditional Chinese medicine has been promoted as a treatment for COVID-19, despite a lack of evidence for its efficacy. **CHINE NOUVELLE/SIPA/Shutterstock**

There are currently no proven treatments for the deadly respiratory disease caused by the new coronavirus, although many countries are trialling existing and experimental drugs. So far, only one — the antiviral remdesivir — has been shown, in randomized control trials, to have some potential to speed up recovery.

In China, senior government officials and the state media are pushing a range of traditional Chinese medicine (TCM) as being effective at alleviating COVID-19 symptoms and reducing deaths

from the disease. However, there are no rigorous trial data to demonstrate that the remedies work.

Although the efficacy of some TCM remedies for COVID-19 is being tested, some researchers say the trials have not been rigorously designed and are unlikely to produce reliable results. Government officials and TCM practitioners deem the remedies safe because some have been used for thousands of years, but significant side effects have been reported.

"We are dealing with a serious infection which requires effective treatments. For TCM, there is no good evidence, and therefore its use is not just unjustified, but dangerous," says Edzard Ernst, a UK-based retired researcher into complementary medicines.

Other world leaders have promoted unproven treatments for COVID-19. US President Donald Trump has pushed the use of hydroxychloroquine, an antimalarial drug with significant potential side effects, whose effectiveness against COVID-19 is still being studied. And the president of Madagascar, Andry Rajoelina, has also claimed that a herbal drink can cure people of COVID-19.

But those leaders' claims have been criticized by scientists in their countries. By contrast, in China, criticism of TCM is muted. The industry is worth billions of dollars per year, and receives aggressive government support.

'Noxious dampness'

TCM is based on theories about qi, said to be a vital energy that helps the body to maintain health. Zhang Boli, president of the Tianjin University of Traditional Chinese Medicine and a member of the national team leading China's response to the coronavirus outbreak, said the severe cases could be attributed to a "noxious dampness," which can cause qi to stagnate.

By March, TCM remedies constituted some of China's health ministry's recommended treatments for COVID-19, and included a couple of dozen pills, powders, injectable therapies and recipes to make herbal teas, known as decoctions.

According to Chinese state media, the State Administration of Traditional Chinese Medicine says three formulas and three medicines "have proved" effective treatments for the disease. The newspaper *China Daily* has reported that "comparative experiments" showed that a group of people with COVID-19 who took Jinhua Qinggan, herbal granules developed to combat H1N1 influenza in 2009, got better faster than those who did not take the capsules, and tested negative for the new virus more than two days sooner. No further details were provided. Another comparative study described in *China Daily* reported that injections of Xuebijing, a concoction of five herbal extracts which is supposed to "detoxify and remove blood stasis", reduced the mortality rate of patients with severe illness by 8.8%, when combined with standard medicines.

Huang Luqi, a TCM practitioner and head of the China Academy of Chinese Medical Sciences in Beijing, says that starting in January, he led trials of another three TCM remedies to treat COVID-19, and found that they were safe and effective. On China's clinical-trials website, the treatments are described simply as traditional Chinese medicine. According to the website, one remedy aims to treat COVID-19 symptoms, another to keep mild cases from becoming severe or critical, and a third to reduce the time taken for a patient to test negative for the virus. Huang did not respond to requests for more details, but says the results will be published soon.

Other scientists say there is no convincing evidence that these remedies are effective against COVID-19. Although the trials had control groups, practitioners and patients don't seem to have been blinded to who was receiving the experimental treatment. Double-blind trials are the gold standard for assessing a treatment's efficacy. "Unless evidence can be demonstrated, it is unethical to market

TCM methods with claims of effects," says Dan Larhammar, a cell biologist at Uppsala University in Sweden.

Something not necessarily better than nothing

People's faith in complementary medicines is understandable given that there is no agreement about what works against COVID-19, says Paul Offit, an infectious-disease researcher at the Children's Hospital of Philadelphia in Pennsylvania. But suggesting that people try alternative medicines could do harm, he says. "People think doing something is better than doing nothing. History tells us that's not true."

Several of the 'decoctions' promoted by the health ministry's official COVID-19 treatment guidelines include a herb called ephedra, which contains the stimulant pseudoephedrine. Extracts of the herb containing this substance have been banned in the United States and several European countries after a string of deaths in the 1990s and 2000s among those who used it for dieting or energy enhancement.

Ernst says that without clear evidence that these treatments work and are safe, China shouldn't be sending them to other countries.

"All parts of a package must be proven to work," he says. Although TCM is a very important export item for China, promoting it during the pandemic "seems reckless and dangerous", he says. China has also sent masks and other protective equipment and ventilators to many countries, including the United States, and contributed US$50 million to the World Health Organization (WHO) for its COVID-19 response.)

The WHO initially discouraged the use of traditional remedies to treat COVID-19. For the first months of the outbreak, they were listed on the agency's website as "not effective against COVID-2019 and can be harmful".

The guidance has since been updated and the warning removed. A WHO spokesperson, Tarik Jašarević, says the original statement "was too broad and did not take into account the fact that many people turn to traditional medicines to alleviate some of the milder symptoms of COVID-19". Jašarević says the guidance stresses that there is no evidence that any current medicine — traditional or otherwise — can prevent or cure the disease, and that the WHO does not recommend self-medication with any substance as a prevention or cure for COVID-19.

Criticism of China's own support for TCM treatments for COVID-19 is unlikely to gain a foothold inside the country. In late April, a doctor at a hospital in Hubei province was censured and demoted from his administrative positions after posting online that China's recommendations on COVID-19 treatments, particularly TCM remedies, were not science-based. The doctor told *Nature* that he could not be interviewed on the topic.

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https://bit.ly/3bqyoza

Study reveals most critically ill patients with COVID-19 survive with standard treatment

Majority of even the sickest patients with COVID-19 get better when they receive existing guideline-supported treatment for respiratory failure

Clinicians from two hospitals in Boston report that the majority of even the sickest patients with COVID-19--those who require ventilators in intensive care units--get better when they receive existing guideline-supported treatment for respiratory failure.

The clinicians, who are from Massachusetts General Hospital (MGH) and Beth Israel Deaconess Medical Center, published their findings in the *American Journal of Respiratory and Critical Care Medicine*.

During the COVID-19 pandemic, hospitals around the world have shared anecdotal experiences to help inform the care of affected

patients, but such anecdotes do not always reveal the best treatment strategies, and they can even lead to harm.

To provide more reliable information, a team led by C. Corey Hardin, MD, PhD, an Assistant Professor of Medicine at MGH and Harvard Medical School, carefully examined the records of 66 critically ill patients with COVID-19 who experienced respiratory failure and were put on ventilators, making note of their responses to the care they received.

The investigators found that the most severe cases of COVID-19 result in a syndrome called Acute Respiratory Distress Syndrome (ARDS), a life-threatening lung condition that can be caused by a wide range of pathogens.

"The good news is we have been studying ARDS for over 50 years and we have a number of effective evidenced-based therapies with which to treat it," said Dr. Hardin.

"We applied these treatments--such as prone ventilation where patients are turned onto their stomachs--to patients in our study and they responded to them as we would expect patients with ARDS to respond."

Importantly, the death rate among critically ill patients with COVID-19 treated this way--16.7%--was not nearly as high as has been reported by other hospitals. Also, over a median follow-up of 34 days, 75.8% of patients who were on ventilators were discharged from the intensive care unit.

"Based on this, we recommend that clinicians provide evidence-based ARDS treatments to patients with respiratory failure due to COVID-19 and await standardized clinical trials before contemplating novel therapies," said co-lead author Jehan Alladina, MD, an Instructor in Medicine at Mass General.

Paper cited: Ziehr DR, Alladina J, Petri CR, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study [published online ahead of print, 2020 Apr 29]. Am J Respir Crit Care Med. 2020;10.1164/rccm.202004-1163LE. doi:10.1164/rccm.202004-1163LE

https://bit.ly/2SM4LQ9

Six-month validation behind polymer that prevents biofilm growth

Prevents biofilm formation for over six months

By Alexandra Klein

Introducing carboxybetaine groups into polyurethane to create a zwitterionic polymer has resulted in a material that resists biofilm growth for six months.[1] Making medical devices such as catheters from the polymer could reduce the number of patients that develop associated infections.

Biofilms naturally form when microorganisms land on surfaces. The microorganisms build up into a structured community embedded in a matrix of extracellular polymeric substances. Around 80% of human bacterial infections involve biofilms and their structure makes them highly tolerant to antibiotics.

Many research groups are therefore developing surfaces that microorganisms can't stick to. In 2007, zwitterionic polymers emerged as an exciting possibility after Gang Cheng and his colleagues at the University of Washington, US, demonstrated they could resist biofilm growth for 10 days.[2] The polymer surface resists bacterial adhesion by forming a moisture layer on top, which acts as a physical barrier. However, these materials have mechanical problems, preventing their use in real-world applications.

Now at the University of Illinois at Chicago, Cheng has addressed this by tweaking the anti-fouling properties of a common material, polyurethane. 'Our strategy incorporates a carboxybetaine precursor into polyurethane as a new component or replaces one of the ingredients in the polyurethane synthesis. The synthesis is very simple and the reactants are very, very cheap. Another nice property about this material is that it can be processed by injection moulding or other traditional polymer processing methods.'

The carboxybetaine precursors provide anti-fouling properties by undergoing rapid, self-catalysed hydrolysis to produce a bacteria-repelling zwitterionic layer. Combined with the tuneable mechanical properties of polyurethane, the team have produced a surface that can be adapted for different applications. Previous studies assessed biofilm growth over 24 hours, with the longest study showing two weeks without growth.

Gang's team tested the material in a nutrient-rich medium during six months of constant exposure to *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* and found it completely prevented biofilms from growing.

Source: © Gang Cheng/University of Illinois at Chicago

The carboxybetaine precursors undergo rapid, self-catalysed hydrolysis at the water/material interface and provide critical anti-fouling properties that lead to undetectable bacterial attachment and zero biofilm formation after six months of constant exposure to *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*

'Zero biofilm formation after six months is indeed impressive,' comments chemical engineer Robert Langer from Massachusetts Institute of Techonology in the US. 'The method also appears easy to use. *Pseudomonas aeruginosa and Staphylococcus epidermidis* are relevant for biomedical applications and so these are really significant results.'

Currently, patients don't keep the same urinary catheter for more than three months and replacing them can be painful. Gang is optimistic that the new material might allow medical devices to stay in for longer. 'This material will significantly reduce the rate of medical device-associated infections. If we can solve the biofilm issue, we can reduce the suffering of patients and save lots of lives.'

'We also showed that the material can delay blood coagulation, meaning patients wouldn't have to take anti-coagulant drugs to prevent medical device-induced thrombosis,' adds Gang. The team also suggest it could have environmental applications as an anti-fouling component in marine coatings.

'This is a potentially important contribution since the development of anti-fouling surfaces has been a holy grail in both microbiology and materials science for decades,' says David Williams, the former editor-in-chief of the journal *Biomaterials*, who works at the Wake Forest Institute of Regenerative Medicine in the US. 'We have known about the resistance of some zwitterionic polymers to biofilm formation, but this is the first time this property has been incorporated into engineering polymers such as this polyurethane.'

Gang's team is now focusing on adapting the material and testing it for different applications. 'This direct work took us three years, but it has taken 10 years of our previous ideas for us to reach this, we also stand on the work of the pioneers in the field. Now we are very close to solving this long-standing problem.'

References

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*2 G Cheng et al, Biomaterials, 2009, **30**, 5234 (DOI: 10.1016/j.biomaterials.2009.05.058)*

https://bit.ly/3chLMV9

Hayabusa2's touchdown on Ryugu reveals its surface in stunning detail

High-resolution images and video were taken by Hayabusa2 as it briefly landed to collect samples

日本のニュース

High-resolution images and video were taken by the Japanese space agency's Hayabusa2 spacecraft as it briefly landed to collect samples from Ryugu - a nearby asteroid that orbits mostly between Earth and Mars - allowing researchers to get an up-close look at its rocky surface, according to a new report.

During the touchdown Hayabusa2 obtained a sample of the asteroid, which it will bring back to Earth in December 2020.

The detailed new observations of Ryugu's surface during the touchdown operations help scientists understand the age and geologic history of the asteroid, suggesting that its surface color variations are likely due to rapid solar heating during a previous temporary orbital excursion near the Sun.

On February 21, 2019, after months of orbital observations to select the target location, the Hayabusa2 spacecraft descended to the surface of Ryugu to conduct its first sample collection, picking up surface material from the carbon-rich asteroid. Previous Hayabusa2 observations have shown that Ryugu's surface is composed of two different types of material, one slightly redder and the other slightly bluer.

The cause of this color variation, however, remained unknown.

During Hayabusa2's touchdown, onboard cameras captured high-resolution observations of the surface surrounding the landing site in exceptional detail - including the disturbances caused by the sampling operation. Tomokatsu Morota and colleagues used these images to investigate the geology and evolution of Ryugu's surface.

Unexpectedly, Morota et al. observed that Hayabusa2's thrusters disturbed a coating of dark, fine-grained material that appeared to correspond with the surface's redder materials.

By relating these findings with the stratigraphy of the asteroid's craters, the authors conclude that surface reddening was caused by a short period of intense solar heating, which could be explained if Ryugu's orbit took a temporary turn towards the Sun.

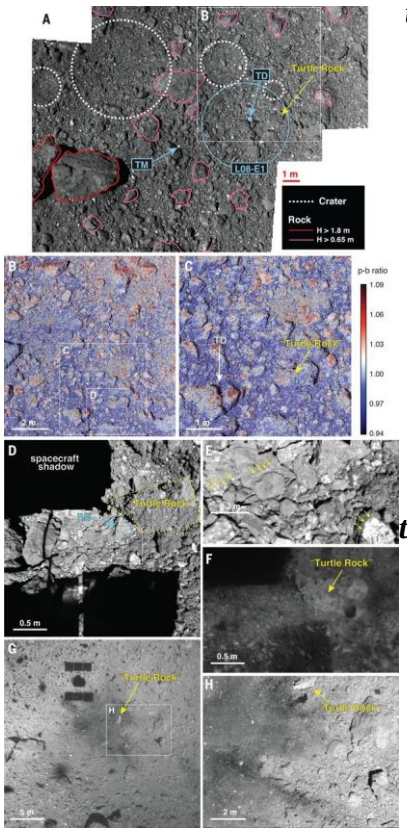


Fig. 2 Touchdown site before, during, and after the touchdown operation. **(A)** ***Boulder and crater map around the touchdown site L08-E1. The light blue arrows indicate the location of the target marker (TM) (4.04°N, 206.01°E) and the touchdown point of the sampler horn (TD) (4.30°N, 206.47°E) (7). The light blue circle indicates the L08-E1 area. The white dashed circles indicate craters. Boulder heights (H) were estimated from their shadow lengths; those with H > 1.8 m are outlined in red and those with H > 0.65 m are outlined in pink. The boulder nicknamed Turtle Rock is indicated by the yellow arrow. The white box indicates the region shown in later panels.*** **(B and C)** ***p-b ratio images (6) calculated from b- and p-band (0.95 μm) images obtained during the touchdown rehearsal operation, from two different altitudes (hyb2_onc_20181015_134707_tbf and hyb2_onc_20181015_134655_tpf). The dashed boxes in (B) indicate regions shown in the other panels.*** **(D)** ***ONC-W1 image obtained during the spacecraft's descent before the touchdown (hyb2_onc_20190221_222859_w1f). The dark, ragged Turtle Rock and an example of bright boulders (BB) with smooth surfaces are outlined in yellow and cyan dashed lines, respectively. The white dashed box indicates the area shown in (E).*** **(E)** ***Close-up of the image in (D), with yellow arrows indicating fresh bright spots at corners and a possible broken plane of a boulder.*** **(F and G)** ***ONC-W1 images obtained ~7 and 47 s after the touchdown, showing debris lifted from the surface (hyb2_onc_20190221_222917_w1f and hyb2_onc_20190221_222957_w1f).*** **(H)** ***ONC-T ul-band (0.39 μm) image obtained at 76-m altitude after the touchdown (hyb2_onc_20190221_223156_tuf). Turtle Rock was lifted clear of the surface by the exhaust from Hayabusa2's RCS thrusters, indicated by the yellow arrows in (F) to (H).***

https://bit.ly/3fxopc8

Possible vaccine for virus linked to type 1 diabetes

Certain virus infections may play a part in the autoimmune attack that leads to type 1 diabetes

According to many observations, certain virus infections may play a part in the autoimmune attack that leads to type 1 diabetes.

Researchers at Karolinska Institutet and at the universities of Jyväskylä and Tampere have now produced a vaccine for these viruses in the hope that it could provide protection against the disease. The study is published 6 May 2020 in the scientific journal *Science Advances*.

While an estimated 50,000 Swedes and 50, 000 Finns live with type 1 diabetes (sometimes known as juvenile diabetes) the causes of the disease remain unknown. There is a genetic component, but also environmental factors are needed for the disease to develop. One such factor believed to be significant in type 1 diabetes is infections caused by an extremely common group of enteroviruses. The sub-group in question is the Coxsackie B (CVB) family and it comprises of six strains that can give rise to the common cold. However, CVBs can also cause more serious infections leading to diseases including myocarditis and meningitis.

According to many scientific observations, one hypothesis suggests that CVBs play a part in the development of type 1 diabetes. The disease is characterised by an autoimmune attack on the insulin-producing beta cells in the pancreas and it is possible that the virus infection somehow initiates this attack by the immune system.

Epidemiological studies, in which children with a genetic risk profile for type 1 diabetes were monitored by blood tests over a period of many years, indicate that CVBs could be a pathogenic contributor. There are also autopsy observations suggesting that CVBs might be involved in the development of type 1 diabetes. This, however, remains hypothetical as the connection is yet to be proven, albeit it is a hypothesis that is well-established amongst diabetes researchers.

Vaccine protects against all six known strains of CVB

Researchers at Karolinska Institutet, Tampere University and University of Jyväskylä in Finland have now produced a vaccine that protects against all six known strains of CVB. The CVB serotypes to be used in the vaccine had been originally detected in the research performed in Vactech Oy in Tampere. The vaccine was tested in different animal models and was shown to protect mice infected with CVB from developing virus-induced type 1 diabetes.

The researchers then tested the vaccine in rhesus monkeys that have very similar genetics to humans. In these animals, the vaccine worked well and induced antibodies to CVB suggesting it could protect against the virus. An American pharmaceutical company is now going to perform clinical studies where they will test the vaccine in human subjects.

Assuming the vaccine is safe in initial trails, the plan is to use the vaccine in children with a genetic risk profile for type 1 diabetes. The researchers write that if the number of children that develop type 1 diabetes decreases after vaccination or if none develop the disease it will confirm that CVB are a triggering environmental factor. "Our hope is that the vaccine will prove effective against CVB infections and that it will then be possible to administer it to children," says Malin Flodström-Tullberg, professor of type 1 diabetes at the Department of Medicine, Karolinska Institutet, Huddinge, and the study's corresponding author.

"It would be fantastic if the cases of type 1 diabetes that we currently suspect are caused by the Coxsackievirus could be prevented, though it's impossible right now to say what percentage of type 1 diabetes cases would be effected. At the same time, the vaccine would give protection against myocarditis, which can have a more severe course in both children and adults, and against many kinds of cold, which keep many people away from school and work."

"The research groups associated with this work have done fruitful collaboration already a longer time, to understand the infection mechanisms of enteroviruses and to develop vaccines and antivirals to combat enteroviruse infection", says Docent Varpu Marjomaki

from the University of Jyvaskyla. Marjomaki is working also at Nanoscience Center at the University of Jyvaskyla.

The study was financed with grants from Business Finland, the Academy of Finland, the Swedish Childrens' Diabetes Fund and the Strategic Research Programme in Diabetes at Karolinska Institutet. The US pharmaceutical company conducting the tests is Provention Bio, for which Malin Flodström Tullberg is scientific advisor. The patent for the vaccine has been in-licensed from the Finnish company Vactech Oy, of which Heikki Hyöty, professor at Tampere University and co-author of the study, was one of the founders.

https://bit.ly/3fvSJUF

Scientists report lunar carbon emissions

And that raises questions about the Moon's past.

Japanese scientists have reported observing carbon ions persistently emitting from the lunar surface.

Given that the prevailing theory for the Moon's formation strongly relies on the notion of a volatile-depleted modern Moon, they say, these findings could have far-reaching implications for our understanding of how it actually came to exist.

"Our estimates demonstrate that indigenous carbon exists over the entire Moon, supporting the hypothesis of a carbon-containing Moon, where the carbon was embedded at its formation and/or was transported billions of years ago," they write in the journal *Science Advances.*

Lead author Shoichiro Yokota, from Osaka University, says early analyses of samples from the Apollo lunar missions led scientists to believe that volatile elements were a thing of the Moon's past. However, analyses in the last decade have challenged this "dry" Moon hypothesis, revealing the presence of volatile water and carbon in volcanic lunar glass.

To assess whether indigenous carbon exists on the present-day Moon, Yokota and colleagues used a map of lunar carbon ion emissions derived from observation data taken by the KAGUYA lunar orbiter over 18 months.

Speculating that there may be an additional, external source for the carbon emissions observed by the orbiter, they estimated the average carbon atoms from the solar wind (the flow of charged particles from the Sun) and from collisions with volatile-rich micrometeoroids, both of which supply carbon to the Moon.

They determined that neither source is capable of supplying the quantity of carbon atoms the Moon regularly emits.

They also report regional differences in lunar carbon ion emissions, with the Moon's large, basaltic plains emitting far more carbon than the highlands – differences they say can best be explained by ancient stores of carbon rather than contributions from outside sources.

Yokota and colleagues say their study also suggests that volatile particles emitted from other small bodies in the Solar System could be effectively observed using ion instruments.

"We, thus, plan to perform secondary ion observations around Mercury and Phobos during the BepiColombo/Mercury Magnetospheric Orbiter and the Martian Moons eXploration missions, respectively," they write.

https://bit.ly/2WBIpSq

An optical brain-to-brain interface supports information exchange for locomotion control

An optical Brain-to-Brain interface (BtBI) enables a Master mouse to control the locomotion of an Avatar mouse.

Communications between two human or animal individuals conventionally depend on sensory systems for vision, audition, olfaction, or touch. Science fiction has popularized the potentials of directly transmitting information between brains for locomotor control. For example, in the 2009 film Avatar, humans use their minds to remotely control the brains of Na'vi-human hybrids to navigate in the real world.

Several recent studies proposed the possibility of retrieving electrophysiological signals from one brain to influence the neuronal activity in another brain through electrical or transcranial magnetic stimulation, suggesting the exciting concept of direct information exchange between brains through the Brain-to-Brain interfaces (BtBIs). However, BtBIs have thus far required the use of demanding techniques for long-term, multi-channel recordings to decode the information from an encoder individual, and has been limited by low rates of information transmission to a target neural circuit.

Multi-channel single-unit recordings are technically challenging and often lack cell-type specificity. EEG recording are inaccessible to subcortical areas to precisely decode specific intention. Moreover, EEG recordings of steady-state visually evoked potentials require external visual stimulation to generate the brain activity rather than the internal neural activity. Another challenge lies in the need of feeding the electrophysiological information, once decoded, into correct cell types and neural circuits in the target brain.

Due to these technical limitations, the information transfer rates were often in the low range of 0.004-0.033 bits/s. Using a BtBI to control locomotion appears to be particularly difficult, since locomotion involves frequent starts, stops, and continuous changes in velocity at a sub-second scale.

Recently, Dr. Minmin Luo's lab published a research article entitled "An Optical Brain-to-brain Interface Supports Rapid Information Transmission for Precise Locomotion Control" in journal *Science China Life Sciences*. In this work, the authors established an optical BtBI that supports rapid information transmission for precise locomotion control, thus providing a proof-of-principle demonstration of fast BtBI for real-time behavioral control.

In this study, the authors demonstrated an optical BtBIs that used fiber photometry to record the population Ca2+ signals of NI neurons from the Master mouse, and then transformed the signals to blue laser pulses, and finally delivered the laser pulses into the NI of the Avatar mouse (Figure 1A, B). This optical BtBI directed the Avatar mice to closely mimic the locomotion of their Masters with information transfer rate about three two orders of magnitude higher than previous BtBIs (Figure 1C-E).

This study emphasize the importance of choosing appropriate neural circuits and of choosing suitable circuit-probing technologies when building a high-performance BtBI.

First, the choice of brain structures is important for implementing task-relevant BtBIs. Here the authors collected neuronal signals that precisely report locomotor state and control locomotor speed from the genetically-identified NMB neurons in the NI of the pons.

Second, the choice of fiber photometry of Ca2+ signals offers several advantages: 1) it stably records the population neuronal activity of specific cell-type that performs similar functions; 2) it has high signal-to-noise ratio (SNR); 3) it is easy to implement, since it bypasses the challenging task of multi-channel single-unit recording from behaving animals and obviates the need for the extensive decoding of information from large datasets.

Finally, the authors used optogenetic stimulation, which also enjoys the advantage of fine-tuning the activity of a genetically defined set of neurons in a given brain area.

In summary, this study demonstrated an optical brain-to-brain interface that supports rapid information transmission for precise locomotion control, and represented a major step toward realizing the full potential of BtBIs.

Lihui Lu from Dr. Minmin Luo's lab is the first author of this study. Ruiyu Wang contributed to computer programs for information decoding. Dr. Minmin Luo the co-corresponding authors. The work was completed in Luo's group at the National Institute of Biological Science, Beijing and Chinese Institute for Brain Research, Beijing.

Lu, L., Wang, R., and Luo, M. (2020). An optical brain-to-brain interface supports rapid information transmission for precise locomotion control. Sci China Life Sci 63, https://doi.org/10.1007/s11427-020-1675-x

https://bit.ly/3fC43yH

Positive Tests For Recovered Virus Patients Are Not Reinfections, WHO Says

Still expelling dead lung cells rather than getting a new infection

Coronavirus patients declared recovered who later test positive for the disease are still expelling dead lung cells rather than getting a new infection, the World Health Organisation (WHO) told AFP on Wednesday. South Korean health officials reported more than 100 such cases in April, raising concerns that patients who had recovered could become reinfected.

"We are aware that some patients test positive after they clinically recover," a WHO spokesperson told AFP, without making specific reference to the South Korean cases. "From what we currently know – and this is based on very recent data – it seems they these patients are expelling left over materials from their lungs, as part of the recovery phase."

People infected with the new coronavirus build up antibodies starting a week or so after infection or the onset of symptoms, research has shown. But it is still not clear, experts say, whether the body systematically builds up enough immunity to ward off a new attack by the virus or, if it does, how long such immunity lasts.

As for the recovered patients who tested negative and then, weeks later, positive, more research is needed, according to the WHO.

"We need systematic collection of samples from recovered patients to better understand how long they shed live virus," the spokesperson said. "We also need to understand if this means they can pass the virus to other people – having live virus does not necessarily mean it can be passed to another person."

In a recent interview with BBC, infectious disease epidemiologist Maria Van Kerhove, part of the WHO's Health Emergencies Program, explained the "dead cell" scenario.

"As the lungs heal, there are parts of the lung that are dead cells that are coming up. These are fragments of the lungs that are actually testing positive," she said. "It is not infectious virus, it's not reactivation. It is actually part of the healing process." "Does that mean they have immunity? Does that mean they have a strong protection against reinfection? We don't know the answer to that yet."

For some viruses, such as the measles, those who contract it are immune for life. For other coronaviruses such as SARS, immunity lasted from a few months to a couple of years. The pandemic has now killed more than 257,000 people globally and officially infected nearly 3.7 million, although with only the most serious cases being tested the number is believed to be far higher.

https://bit.ly/3bq5X4F

Coronavirus Might Exploit 'Silent' Mutations Hidden in People, Scientists Think

Why are some people barely affected by coronavirus, while others become gravely ill even though they are young and healthy?

Amelie Bottollier-Depois, AFP

Scientists are searching for answers in patients' genes, looking for mutations that affect their immune response in the hope of finding new treatments. As more people become infected with the virus, a rough profile of a severely-affected patient has emerged: older, with underlying illnesses and more likely to be male.

But that is far from the full picture.

Intensive care units around the world have also treated a minority of people who are under 50 with no underlying medical problems.

These roughly five percent of patients are the ones that interest geneticist Jean-Laurent Casanova.

"Someone who could have run the marathon in October 2019 and yet in April 2020 is in intensive care, intubated and ventilated," he told AFP.

Casanova, director of the human genetics of infectious diseases laboratory jointly based at the Imagine Institute in Paris and Rockefeller University in New York, wants to find out if they have rare genetic mutations.

"The assumption is that these patients have genetic variations that are silent until the virus is encountered," he said.

Casanova co-founded the COVID Human Genetics Effort, which is seeking to study the genome of these severely-ill younger patients in places like China, Iran, Europe, North America and Japan.

The group is also looking at people who do not become infected despite repeated exposure.

Their research is among a huge global effort involving dozens of labs scouring the genomes of COVID-19 patients for variations that might explain why some people get sicker than others - and potentially help develop anti-viral therapies.

Not just 'bad luck'

Gene mutations have been found to make people more vulnerable to a range of infectious diseases, from influenza to viral encephalitis. They can sometimes also offer protection.

In the mid-1990s researchers discovered that certain rare mutations of a single gene (CCR5) effectively stopped people from becoming infected with HIV.

The discovery gave researchers a greater understanding of the way the virus worked and paved the way for the development of new treatments.

In the past, whether a person became seriously ill with a particular disease was often put down to "bad luck", said Jacques Fellay, a professor of human genomics of infectious diseases at the Federal Polytechnic of Lausanne.

"Today, we have the capacity to go and dissect the genome of these people and see if they have a rare mutation which could make them particularly susceptible" to the new coronavirus, he told AFP.

But differences in immune response are often caused by multiple genetic factors, Fellay said, likening the body's defence mechanism to a mechanical watch.

"There can be a grain of sand in the cogs. Among a group of patients, each of these grains of sand can be different, but produce the same result", he said.

Treatment hope

This complexity means "we need to have a very large sample and collaboration, and the ability to repeat the observation to be confident about the results," said Mark Daly, director of the Institute for Molecular Medicine Finland.

Daly is one of the scientists behind the COVID-19 Host Genetics Initiative, a large-scale global collaboration involving some 150 research centres.

The project aims to recruit at least 10,000 patients and share findings. Researchers hope to have "very useful information" by the summer, he said, although the timeline is by no means guaranteed.

Ideally the work would lead to treatments.

"There are a huge number of medicines available that target specific genes," Daly told AFP. "If we find a genetic clue that points us to a gene that already has a medication developed, then we could simply repurpose the drug."

But the process could be much more complicated. Researchers may find mutations in genes that have not had drugs developed for them - potentially lengthening the time to create a treatment, said Fellay.

Or worse, they may find that the mutations are not "actionable", or that interventions would create too many side effects.

Discovering the genetic mutations behind immune responses to COVID-19, then, is only the beginning.

"Genetics is a tool for exploring biology, but the resulting treatment, there is nothing genetic about it," he said.

https://bit.ly/3biRTHq

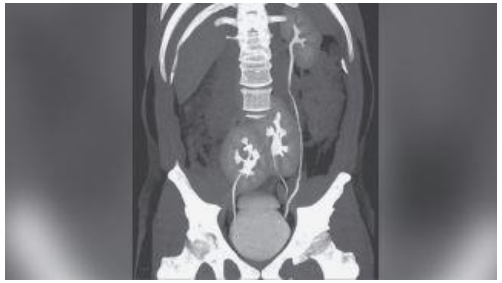
Man with back pain finds out he has 3 kidneys

Having three kidneys is rare, with fewer than 100 cases reported in the medical literature.

By Rachael Rettner - Senior Writer

When a Brazilian man went to the doctor complaining of low-back pain, his doctors got a surprise: They discovered that the man had not two, but three kidneys — a very rare condition.

To figure out the cause of the 38-year-old man's severe pain, doctors at the Hospital do Rim in São Paulo, Brazil, performed a CT scan to evaluate the area, according to a report of the case, published Wednesday (May 6) in The New England Journal of Medicine (NEJM).



***A man in Brazil learned he had three kidneys after receiving a CT scan for low-back pain. Above, the CT scan showing the man's three kidneys: A normal-appearing kidney on the man's left side, and two kidneys fused at the pelvis.* (Image: © The New England Journal of Medicine ©2020)**

The scan showed the man had a herniated or "slipped" disk, a relatively common condition in which part of a cushion-like disk between the spinal vertebrae moves out of place.

But it wasn't just the herniated disk that caught the doctors' attention. They couldn't help but notice that the man had an unusual anatomical feature. Instead of the usual two kidneys seen in a typical person, the man had three: a normal-looking kidney on his left side and two fused kidneys located near the pelvis, the report said. The man didn't have any symptoms of a kidney problem, and the organs appeared to be working normally.

Usually, each kidney is connected to the bladder through a single duct called a ureter. In the man's case, one of the pelvis kidneys was directly connected to the bladder via a ureter. However, the ureter of the other pelvis kidney joined the ureter of the normal, left-side kidney before it entered the bladder.

Having three kidneys is rare, with fewer than 100 cases reported in the medical literature, according to a 2013 report of a similar case published in The Internet Journal of Radiology. The condition is thought to arise during embryonic development, when a structure that typically forms a single kidney splits in two.

Because the condition doesn't usually cause symptoms, people typically don't know they have it unless it's discovered by accident through unrelated medical tests, the authors of the NEJM report said. The man didn't need any medical attention for his extra kidney. But he did receive oral painkillers for his back pain, the report said.

https://bit.ly/2WFTIZU

By the third day most with COVID-19 lose sense of smell

University of Cincinnati researcher says antiviral treatments may help most if patients identified early

A University of Cincinnati researcher says a study of COVID-19 patients shows loss of the sense of smell is most likely to occur by the third day of infection with the novel virus. Most of these patients are also experiencing a loss of the sense of taste.

The prospective, cross sectional telephone study examined characteristics and symptoms of 103 patients who were diagnosed with COVID-19 over a six-week period at Kantonsspital Aarau in Aarau, Switzerland. Patients were asked how many days they had COVID-19 symptoms and also asked to describe the timing and severity of loss or reduced sense of smell along with other symptoms.

At least 61% of the patients reported reduced or lost sense of smell, says Ahmad Sedaghat, MD, PhD, an associate professor in the UC College of Medicine's Department of Otolaryngology-Head and

Neck Surgery and an UC Health physician specializing in diseases of the nose and sinuses, who was the principal investigator of the study. The mean onset for reduction or loss in the sense of smell was 3.4 days.

The findings are available online in the scholarly journal *Otolaryngology-Head and Neck Surgery*. The first author of the research is Marlene Speth, MD, at the Switzerland hospital.

"We also found in this study that the severity of the loss of smell is correlated with how bad your other COVID-19 symptoms will be," says Sedaghat. "If the anosmia, also known as loss of smell, is worse, the patients reported worse shortness of breath and more severe fever and cough."

"Should that concern patients?" says Sedaghat. "The relationship between decreased sense of smell and the rest of the COVID-19 is something to be aware of. If someone has a decreased sense of smell with COVID-19 we know they are within the first week of the disease course and there is still another week or two to expect."

Sedaghat says an experimental antiviral drug, remdesivir, developed by Gilead Sciences to initially treat Ebola, is showing some promise in treating COVID-19 patients. It has been granted emergency approval by the U.S. Food and Drug Administration to treat severely ill COVID-19 patients, since a National Institutes of Health-sponsored clinical trial showed that patients experienced a shorter recovery time when taking remdesivir compared to a placebo.

Sedaghat says that having an available antiviral treatment for COVID-19 may mean it's much more important to have an indicator of prognosis and how far the disease has progressed in patients.

"Antiviral medications have historically worked best when given early during a viral infection. The same is hypothesized to be true for remdesivir," says Sedaghat. "Our study indicates that a decreased sense of smell may be an indicator of patients early in the disease course as well as those who may go on to develop more severe symptoms, like shortness of breath, later on. "Once remdesivir becomes more widely available, decreased sense of smell may therefore identify patients who would be excellent candidates for the medication," he says.

Sedaghat cautions that while the loss of smell is an indicator of COVID-19, it's not the only factor. "When you start to experience serious symptoms of COVID-19 which include shortness of breath and respiratory distress, that's when you should become alarmed," he adds.

The study also found that younger patients and women in the study were also more likely to experience a decreased loss of smell, says Sedaghat.

Also, about 50% of study patients experienced a stuffy nose and 35% experienced a runny nose. Sedaghat says this is important because previous studies indicated that these nasal symptoms were rare in COVID-19 and these symptoms were attributed to allergy and not the novel coronavirus.

"This just means that greater awareness is needed of COVID-19's nasal symptoms so people are not running around sneezing in public and thinking it is okay since this is just allergies," says Sedaghat. "It very well could be COVID-19 and wearing masks as protective gear for others you encounter is a good idea."

Sedaghat says understanding more about loss of smell and COVID-19 is important for a public health perspective.

"No one is going to die because of a loss of the sense of smell and it's not the symptom that will kill anyone," says Sedaghat. "However, it is important because it helps us to identify these COVID-19 patients as asymptomatic carriers so they don't spread the disease to others. Now we can potentially identify them early

during the disease to start antiviral medications and ultimately maximize our ability to effectively treat these patients."

Other co-authors of the study include Isabelle Gengler, MD, UC Department of Otolaryngology-Head and Neck Surgery, along with Thirza Singer-Cornelius, MD; Michael Oberle, PhD, and Steffi Brockmeier, MD, all from Kantonsspital Aarau.

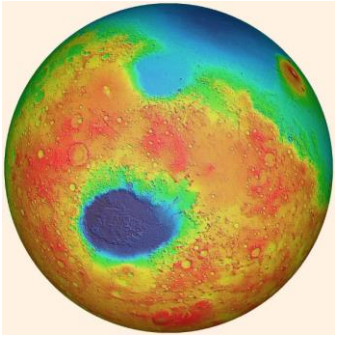
Funding for the study came from Kantonsspital Aarau, Aarau, Switzerland.

https://bit.ly/2AcGI6h

Deep, Perennial or Semi-Perennial Rivers Flowed on Early Mars

Evidence of an incredibly large lake and a network of ancient rivers, deltas and outflow channels

While the present-day Martian surface is generally dry and cold, its sedimentary rocks contain compelling evidence for the former presence of liquid water. According to a new analysis of orbital images of 3.7-billion-year-old sedimentary layers at Izola mensa, an outcrop in the northwestern rim of the Hellas impact crater on Mars, deep rivers were active in this region for over 100,000 years.



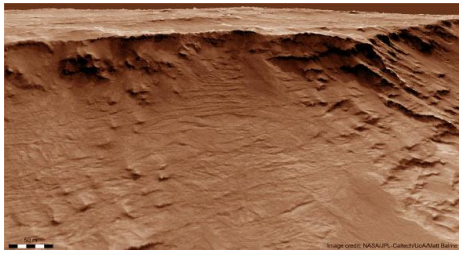
This false-color map, produced by the Mars Orbiter Laser Altimeter (MOLA), depicts the topography of the Martian surface. Hellas basin, the large, dark blue region below the center, has a diameter of 1,430 miles (2,300 km), and is one of the largest identified impact craters both on Mars and within the Solar System. It is thought to have formed some 4 billion years ago. **MOLA Science Team.**

Hellas Planitia is the largest well-preserved impact structure on Mars and the third or fourth largest in the Solar System. It spans 2,300 km (1,430 miles) across in the Martian southern hemisphere, a region that is much more heavily cratered and higher in average elevation than the northern hemisphere. The depth of Hellas from its bottom to its inner rim is more than 4 km (2.5 miles). To put this in perspective, the depth of the Grand Canyon in the United States is roughly 1.6 km (1 mile).

It contains a variety of 3.7-billion-year-old sedimentary plains, overlain by 3.3-billion-year-old lava flows. Landforms preserved on its surface provide evidence of an incredibly large lake and a network of ancient rivers, deltas and outflow channels.

"The extremely high resolution imagery allowed us to 'read' the rocks as if you are standing very close to the cliff," said Dr. Francesco Salese, a geologist at Utrecht University and senior scientist in the International Research School of Planetary Sciences.

"Unfortunately, we don't have the ability to climb, to look at the finer-scale details, but the striking similarities to sedimentary rocks on Earth leaves very little to the imagination."



Channel-forms preserved in sedimentary layers in Hellas Planitia on Mars. **NASA / JPL-Caltech / University of Arizona / Matt Balme.**

In the study, Dr. Salese and colleagues examined sedimentary-stratigraphic architecture of a 1,500-m (4,921-foot) wide, 190-m (623-foot) thick sedimentary succession at Izola mensa.

They used images captured by the High Resolution Imaging Science Experiment (HiRISE) camera on NASA's Mars Reconnaissance Orbiter.

"Here on Earth, the stratigraphy (i.e. the order and position) of sedimentary rocks has been used by geologists for generations to place constraints on what conditions were like on our planet millions or even billions of years ago," said Dr. William McMahon, a geologist at Utrecht University.

"Now we have the technology to extend this methodology to another terrestrial planet, Mars, which hosts an ancient sedimentary rock record which extends even further back in time than our own."

The team's observations and analysis favor steady water discharges that are most consistent with a precipitation-driven hydrological cycle.

"Our study demonstrates sustained river deposition on Mars 3.7 billion years ago," Dr. Salese said. "Such perennially flowing rivers would require an environment capable of maintaining large volumes of water for extensive time-periods, and almost certainly necessitated a precipitation-driven hydrological cycle."

"More in line with slower climatic change, and less in line with catastrophic hydrologic events. This kind of evidence, of a long-lived watery landscape, is crucial in our search for ancient life on the planet."

"For the first time, orbital data has allowed us to examine, through detailed high-resolution architectural analysis, a large outcrop, and draw reliable paleoenvironmental interpretations based on sedimentary-stratigraphic evidence."

The findings were published in the journal *Nature Communications*.

F. Salese et al. 2020. Sustained fluvial deposition recorded in Mars' Noachian stratigraphic record. Nat Commun 11, 2067; doi: 10.1038/s41467-020-15622-0

https://bit.ly/3clYkuy

Pangolins may possess evolutionary advantage against coronavirus

The exotic animal's genome could point to possible treatment options for COVID-19 in humans

Similar to how a smoke detector sounds off an alarm, certain genes sense when a virus enters the body, alerting of an intruder and triggering an immune response in most mammals. But, according to a recent study published in *Frontiers in Immunology*, pangolins - mammals which resemble an anteater with scales, lack two of those virus-sensing genes. The finding is significant because while pangolins can be carriers of coronavirus, they appear able to tolerate it through some other unknown mechanism. Understanding their evolutionary advantage may point to possible treatment options for coronavirus in humans.

Researchers focused on pangolins because the exotic animal may have transmitted the virus to humans last year, creating the interspecies jump required for the current COVID-19 pandemic to take hold (bats have also been identified as possible agents of infection). To obtain their results, they analyzed the genome sequence of pangolins and compared it to other mammals including humans, cats, dogs, and cattle.

"Our work shows that pangolins have survived through millions of years of evolution without a type of antiviral defense that is used by all other mammals," says co-author Dr. Leopold Eckhart, of the Medical University of Vienna in Austria. "Further studies of pangolins will uncover how they manage to survive viral infections, and this might help to devise new treatment strategies for people with viral infections."

In humans, coronavirus can cause an inflammatory immune response called a cytokine storm, which then worsens outcomes. Pharmaceutical suppression of gene signaling, the authors suggest, could be a possible treatment option for severe cases of COVID-19. Eckhart cautions though that such a remedy could open the door to secondary infections. "The main challenge is to reduce the response to the pathogen while maintaining sufficient control of the virus," he says. An overactivated immune system can be moderated, Eckhart says, "by reducing the intensity or by changing the timing of the defense reaction."

While the study identified genetic differences between pangolins and other mammals, it did not investigate the impact of those differences on the antiviral response. Scientists don't yet understand how exactly pangolins survive coronavirus, only that their lack of these two signaling genes might have something to do with it. Eckhart adds that another gene, RIG-I, which also acts as a sensor

against viruses, should be studied further as it could defend against coronaviruses. The study offers a starting point to better understand coronavirus's characteristics, the body's response, and the best options for treatment.

Notes to Editors

Please link to the original research article in your reporting:
https://www.frontiersin.org/articles/10.3389/fimmu.2020.00939/full
Corresponding author: Leopold Eckhart

https://wb.md/3dBBm33

Acute Flaccid Myelitis Tends to Spike in Even-Numbered Years. This Summer Could Bring Another Surge

Flaccid weakness that results from damage to the longitudinal gray matter in the spinal cord.

Sarah E. Hopkins, MD, MSPH

This transcript has been edited for clarity.

I am Sarah Hopkins. I'm an assistant professor of clinical neurology and an attending neurologist at the Children's Hospital of Philadelphia and the University of Pennsylvania, Perelman School of Medicine.

Today I'm going to talk about acute flaccid myelitis (AFM) — its characteristics, diagnostic testing, early management, complications, and outstanding questions that we're hoping to address in the upcoming year.

Characteristics

AFM is the acute onset of flaccid weakness that results from damage to the longitudinal gray matter in the spinal cord. [The Centers for Disease Control and Prevention (CDC) began tracking AFM in 2014] and since then, we've seen an increase in cases every 2 years in the United States. These children typically present in the setting of a current or very recent febrile illness, usually with upper respiratory infection symptoms, although sometimes with gastrointestinal symptoms.

Hallmarks include proximal weakness in the shoulders or hips. This manifests as weakness with shoulder elevation; children can't give a high five, can't raise both their arms.

Hip strength is also compromised. To assess hip strength, you can ask the child to get up from a seated position on the floor.

The child often has pain in the affected extremity and sometimes subtle sensory abnormalities as well.

Diagnostic Testing

Diagnostic testing includes MRI of the spinal cord to look for gray matter abnormalities that would be classic for AFM. Abnormalities often involve the anterior horn cells.

You also will want to identify the virus that may be associated with this presentation. We recommend testing for respiratory viruses, including an enteroviral polymerase chain reaction (PCR) of the patient's respiratory secretions, specifically a nasal pharyngeal swab. Typically, we also consider a spinal tap to look for CSF pleocytosis.

Complications

One reason for identifying AFM early is that once these children start to develop weakness, it can progress over hours to days and cause respiratory compromise. Especially in patients with upper extremity involvement, and as with any lesion involving the upper cervical spine, you want to watch closely, observing the patient in the hospital to be sure their breathing is not impaired.

Management

Right now we don't have a medicine that clearly alters the course of AFM. A mouse model demonstrated that intravenous immunoglobulin (IVIG) was helpful if given early. Because of this, we are trying to give IVIG therapy as early as possible. Again, this is not a proven treatment. We don't currently have a proven treatment.

If we see a lot of spinal cord swelling, we consider giving steroids, and some also consider giving plasma exchange.

Unanswered Questions

We know that some of these patients have had enterovirus infections. The one that's the most suspect is enterovirus D68, which was circulating at the time of the initial emergence of AFM in 2014 and has been associated with some of these cases. Another one that may be a culprit for some cases is enterovirus A71.

There's still a lot to be learned to firm up this connection so that we can consider what additional therapies would be appropriate. To that end, upcoming studies include a National Institutes of Health AFM natural history study, which is a multisite study that will be conducted throughout the United States.

Sarah E. Hopkins, MD, MSPH, is a pediatric neurologist and section head for Multiple Sclerosis and Neuroinflammatory Disorders at Children's Hospital of Philadelphia. Her research includes funding from the Centers for Disease Control and Prevention related to AFM surveillance.

https://bit.ly/2SQyzuU

How Long Was Venus Habitable?

Climate simulations of Venus's history could provide insights into the habitability of Earth and of exoplanets.

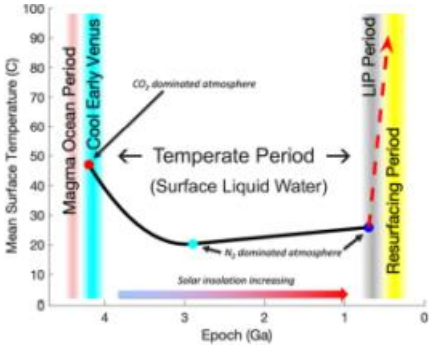
By Kate Wheeling 8 May 2020

Earth and Venus are "sister worlds," sharing a similar size, mass, and bulk composition. You wouldn't want to visit modern-day Venus, though, with its atmosphere of carbon dioxide and nitrogen and surface temperatures hovering around 450°C. But our neighbor probably wasn't always so inhospitable.

Deciphering what early Venus looked like isn't easy—in part because the planet's surface is relatively young, just 300–700 million years old—but indications from the Pioneer Venus mission suggest that its atmosphere once contained more water than it does today. Venus also might have hosted liquid water at its surface, as well as plate tectonics and a stable, temperate climate; some studies even indicate that Venus's climate may have been more stable than early Earth's, avoiding Earth's icy snowball periods.

Theories abound about what led to Venus's drastic transformation: A gradually warming Sun may have left the planet hot and desiccated after a short period of habitability, or a very early magma ocean and an atmosphere of carbon dioxide and steam could have given way to the planet's current state nearly 4 billion years ago.

In a new study, though, *Way and Del Genio* provide evidence that a shallow water ocean and habitable conditions may have persisted on Venus for as long as 3 billion years, until volcanic large igneous provinces (LIPs) emerged simultaneously and ended the planet's temperate period.



This representation of Venus's possible climate history, based on new research, indicates that surface water and habitable conditions might have persisted on Venus's surface for several billion years (Ga) before simultaneous volcanic eruptions of large igneous provinces (LIP) over the past few hundred million years led to the planet's current hothouse state. Data points represent mean surface temperatures at 1 bar of atmospheric pressure. The red dashed arrow represents the transition to a runaway greenhouse atmosphere. **Michael Way, NASA Goddard Institute for Space Studies**

The team ran several simulations of Venus's history using NASA's ROCKE-3D (Resolving Orbital and Climate Keys of Earth and Extraterrestrial Environments with Dynamics) general circulation model to examine how variations in the planet's rotation rate and surface water levels might have influenced its early climate. Assuming that Venus's early atmosphere, like early Earth's, was carbon rich and cool and that its rotation rate was slow, the team found that Venus's climate could have been stable for most of the planet's more than 4-billion-year history—a strike against the gradually warming Sun theory.

The authors believe that simultaneous eruptions of LIPs over the past few hundreds of millions of years could have led to a runaway greenhouse effect by releasing large amounts of carbon dioxide into the atmosphere. The resultant drying of the planet's surface could have driven it into a new interior-surface dynamics regime, with newly exposed basalts—evident on Venus today—acting as an efficient oxygen sink.

In Earth's past, LIPs have emerged sequentially in a random stochastic process, rather than simultaneously, which the authors note is "fortuitous for life as we know it today." But not enough is known about Venus's interior to speculate whether an uninhabitable end state is the inevitable product of internal processes on Venus-like planets or even on Earth for that matter. Researchers need more observations from Venus's surface to better constrain its early history and further challenge the magma ocean theory.

Ultimately, a better understanding of Venus's history will provide insights into both terrestrial processes and those of exoplanets, including whether the window of habitability is wider than currently thought.

(Journal of Geophysical Research: Planets, https://doi.org/10.1029/2019JE006276, 2020)
—Kate Wheeling, Science Writer

Citation: *Wheeling, K. (2020), How long was Venus habitable?, Eos, 101, https://doi.org/10.1029/2020EO142936. Published on 08 May 2020.*

https://bit.ly/2Wkwp96

A Much-Hyped COVID-19 Drug Is Almost Identical to a Black-Market Cat Cure

Cat owners are resorting to China's underground marketplace to buy antivirals for a feline coronavirus.

Sarah Zhang

When Robin Kintz's two kittens, Fiona and Henry, contracted a fatal cat disease last year, she began hearing of a black-market drug from China. The use of the drug, known as GS-441524, is based on legitimate research from UC Davis, but the ways to get it seemed much less so. "It was, 'If you want to save your cat, send me thousands of dollars, and I'll DHL you some unmarked vials,'" she says. And she did. Kintz transferred the thousands of dollars, got the unmarked vials from China, and then injected the clear liquid into her dying cats every day for months.

The first remarkable thing, given the nature of the transaction, is that Kintz says the vials actually worked. Henry lived for almost another year, and Fiona made a full recovery. She's still scampering around today, fluffy and alive—a miracle considering that vets had long thought her disease, feline infectious peritonitis, to be incurable and 100 percent fatal. Kintz now runs a 22,000-member Facebook group that helps cat owners using GS-441524. Thousands of cats have reportedly been cured of FIP.

The second remarkable thing is that GS-441524 is almost identical to a much buzzed-about human drug: remdesivir, the antiviral currently our best hope for treating COVID-19, the disease caused by the novel coronavirus. Although early data suggest that the drug shortens recovery time at best, Anthony Fauci has touted remdesivir from the White House. The Food and Drug Administration has authorized it for emergency use. And Gilead Sciences, the company that makes remdesivir, is donating 1.5 million doses of the drug amidst the pandemic.

Henry (L) and Fiona (R) were both treated with GS-441524. Henry died earlier this year, but Fiona is still alive, which her owner Robin Kintz attributes to the drug. (Courtesy of Robin Kintz)

Gilead invented and patented GS-441524, too. Its scientists co-authored the UC Davis studies showing effectiveness against FIP. But the company has refused to license GS-441524 for animal use, out of fear that its similarity to remdesivir could interfere with the human drug's FDA-approval process—originally for Ebola. When that failed, and a global pandemic of a novel coronavirus later arose, the company began testing it against COVID-19. Remdesivir has a

small but clever modification that makes it better at entering cells, but it and GS-441524 work in exactly the same way to inhibit viruses.

FIP is also caused by a coronavirus—not the same one that causes COVID-19, but one that specializes in infecting cats. (Although humans may be able to pass COVID-19 to cats in rare cases, humans cannot get FIP from cats.) In most cats, this feline coronavirus, or FCoV, causes mild diarrhea or no symptoms at all. But in a small minority of cases, the virus infects white blood cells, and the immune system goes haywire into full-blown FIP. The disease comes in two forms, both fatal: wet, in which the cat's chest or belly swells with fluid, or dry, in which there is no fluid but the cat is still feverish and sick. Eventually, it dies. For decades, vets have had little to offer but euthanasia.

Then GS-441524 came along. Small trials at UC Davis published in 2018 and 2019 suggested that cats were not just having their life prolonged by days or weeks, but were seemingly cured. "It really was a game changer," says Drew Weigner, a veterinarian and the president of the Winn Feline Foundation, which funded some of the UC Davis research. "Three years ago, we told patients, 'Your cat is going to die.' Now we can tell them something else. It's quite a story."

The story of a drug first tested against Ebola (that failed), whose close cousin became a groundbreaking treatment for a cat disease (but only illegally), and that has been resurrected in the pandemic of an entirely new virus underscores the vagaries of drug development. To be clear, while remdesivir is in clinical trials, GS-441524 has not been tested in humans for safety or efficacy against COVID-19. The black-market formulations of GS-441524 are also incredibly expensive. A 12-week regimen for cats can cost upwards of $10,000, depending on the brand, type of FIP, and weight of the cat. Plus, there is no legal way to buy GS-441524 as medicine—not for cats, not for humans.

The drug probably would have never been tested in cats, if not for the fact that Niels Pedersen, a longtime FIP researcher at UC Davis, personally knew the former chief scientific officer of Gilead. The two met 30 years ago, when Gilead was testing antiviral HIV drugs in monkeys and Pedersen was working at a primate research center. But Pedersen's true love has always been cats. He grew up surrounded by them on a poultry farm. A colleague of his warned me, lovingly, that Pedersen was "irascible," and he was difficult to get on the phone. But his voice softened when he talked about taming those barn cats and finding homes for their kittens.

Pedersen became fascinated with FIP in vet school in the 1960s, when it was still a mysterious disease with a mysterious cause. Over the decades, scientists would discover the feline coronavirus behind FIP and then spend years trying but failing to develop a working vaccine. Pedersen ended up devoting his career to the disease. And when the vaccines failed, he began thinking about antivirals, and he began thinking, again, of Gilead. The California-based company specializes in developing antivirals, including Tamiflu, Truvada, and a host of HIV and hepatitis C drugs.

Around five years ago, Pedersen got in touch with his Gilead contact, and the company sent him 25 or 30 molecules, drawn from the large library of drug candidates that pharmaceutical companies typically maintain. Two of the molecules worked marvelously in cat cells infected with the FIP virus: GS-441524 and GS-5734, the latter of which is now better known as remdesivir.

Both GS-441524 and remdesivir work by blocking viral replication. They are nucleoside analogues, meaning they mimic the nucleoside building blocks—A, U, C, or G—that make up the virus's genetic material. Specifically, they mimic "A," and when the virus is tricked into incorporating a GS-441524 or remdesivir molecule

instead of “A”, the replication process gets jammed up. Eventually, no more letters can be added, and the virus cannot replicate. Where the two drugs differ is that remdesivir has an extra phosphate group, a small change that helps it enter a cell and get used in replication. This modification is commonly used to enhance the effectiveness of similar antivirals. “It’s just one of those really clever things that worked perfectly,” says Katherine Seley-Radtke, an antiviral researcher at the University of Maryland, Baltimore County.

For whatever reason, though, this modification did not make much difference in cat cells infected with the FIP virus. Both molecules were effective, so Pedersen decided to pursue the simpler one, GS-441524. He then infected 10 cats with FIP and dosed them with GS-441524. All 10 cats recovered.

“We almost fell out of our chairs,” says Weigner.*This is ridiculous*, he remembers thinking. *This can’t work this well. Wait, wait, stop, go back? It did what?* The initial study was small and under artificial conditions, but in a follow-up field trial of 31 pets with naturally acquired FIP, 25 ultimately made it—an unheard-of recovery rate. Pedersen had previously tested another antiviral out of Kansas State University, but only seven out of 20 cats had gone into remission. Those results seemed impressive at the time, but GS-441524 appeared to be even better.

Pedersen is 76 now, and he has devoted 50 years of his career to FIP research. Finally, it seemed, a cure was at hand. “I felt really good,” he told me, “and I thought this was a good capstone for my career.” But the capstone never materialized, at least not in the way that he expected. Despite the success, Gilead refused to license GS-441524 for use in cats.

While Pedersen was testing GS-441524 in cats, a different virus—a human virus—was raging halfway around the world in West Africa: Ebola. The virus that causes Ebola is not a coronavirus, but remdesivir is unusually broad-acting for an antiviral, and early results against Ebola were promising. So promising, in fact, that the company was eyeing FDA approval of remdesivir in humans.

According to Pedersen, Gilead worried that the cat research could impede the approval process for remdesivir. Because GS-441524 and remdesivir are so similar, any adverse effects uncovered in cats might have to be reported and investigated to guarantee remdesivir’s safety in humans. Gilead’s caution about generating unnecessary cat data is standard industry practice. “One of the rules in drug development is never perform a test you don’t have to, if the results could be problematic,” says Richard Sachleben, a retired pharma-industry researcher. (Gilead declined to comment for this story.)

For Pedersen, the explanation was hard to accept. “It was a blow,” he said. “It hits you very hard, especially when you didn’t see any reason for it.” He still published the studies, as academic researchers do, and results became public in 2018 and 2019.

Not long after, Pedersen began hearing from people in China. One company wanted to license the drug from Gilead, he told me, and it asked Pedersen to be the intermediary. The company failed to get a license but started selling an FIP drug anyway, and its exact formula is unclear. Other companies explicitly advertise their formulations as GS-441524. China has a large base of pharmaceutical manufacturing, and raw GS-441524 is not particularly difficult to synthesize. FIP is also a growing problem in the country as cats—especially purebred cats, which are more prone to the disease—become more popular in China. A black market has sprung up to fill the vacuum left by Gilead.

The use of drugs from China was at first controversial in the FIP community. “I got a lot of hate mail for it. I lost a lot of supporters,” says Peter Cohen, an early supporter of the drugs. Cohen runs ZenByCat, a nonprofit that raises money for two groups funding FIP research, SOCK FIP and the Winn Feline Foundation’s

Bria Fund for FIP Research. Earlier iterations of Facebook support groups, such as FIP Fighters, initially banned any discussion of the black-market drugs too.

Susan Gingrich, a former administrator of that Facebook group, has focused on pressuring Gilead. Gingrich, whose brother is former House Speaker Newt Gingrich, is also the founder of the Bria Fund. Her cat Bria died of FIP in 2005, and she established the fund with donations from her brother and herself and her husband that same year. “It would be so much easier if Gilead would have either marketed it or let another entity market it,” she says. Gingrich bought stock in Gilead after early research into GS-441524 seemed promising. In June 2019, she wrote a letter to Gilead, as well as to President Donald Trump and her congressman and senators in Tennessee, imploring the company to allow animal use of the drug. She says she’s received no response.

When Kintz was trying to save Fiona and Henry, she asked about GS-441524 in one of those Facebook groups that had banned discussion of the drug. Her post in the group went nowhere, but two women privately messaged her with advice. Kintz ended up starting a new group, now called FIP Warriors, so they could exchange tips and feedback on different brands. The group grown to 22,000 members on Facebook—as well as 25 admins and 26 moderators. It has satellite groups in different countries and languages around the world. “It feels like a global corporation sometimes,” says Kintz, who is a design consultant in upstate New York when she’s not running the Facebook group. If she is going to be offline for, say, six hours, she notifies her fellow admins and moderators. The Facebook group has morphed into a 24/7 international organization. FIP Warriors also has a network of emergency group chats for every state. Because shipping from China can take a long time and because the earlier that GS-441524 treatment is started, the better, the emergency chats connect new members with those who have vials of extra GS-441524.

Zina Lemesh, a lawyer and cat breeder in New York, joined the group in February, when her cat Nora grew jaundiced and stopped eating, and her belly swelled up like a bowling ball. Lemesh recognized the signs of wet FIP, and she knew it as a hopeless disease. She was preparing to call her vet about euthansia when she came across the group in a frantic online search for a treatment. She posted an emergency plea for GS-441524. “Within 10 minutes, I was in contact with someone,” she told me. “Within the next two hours, my cat already had shots.” And within a couple days, Nora started eating again. She is almost done with her 84-day regimen. Her swollen belly is completely gone.

“This is a cat mom and an attorney speaking at the same time and I try to balance the two in my brain, which it’s hard,” Lemesh said. On one side is the cat mom who would go to great lengths to save her cat; on the other is the rules-minded lawyer who can’t believe she injected her cat with unlabeled drugs from a stranger. But if it’s between letting Nora die and a small chance at saving her, the choice was clear. Of course, Lemesh told me, she would rather go the legitimate route—if that were an option. “Do you think people would like to send $7,000 to $12,000 to some weird source?” she said. “Or would they prefer to pay their vet?”

The black-market availability of GS-441524 puts veterinarians in a bind. They can’t prescribe the drug or legally buy it for cat owners. Some do agree to help owners with the injections, which can be difficult and painful for the cat. But others want nothing to do with the unapproved drug. Linda Pendergrass-Nethery, who lives in Chattanooga, Tennessee, told me she ended up switching vets. Her first vet refused to help, she said. The second prescribed the sedative gabapentin to mellow out her cat, Sundance, for injections. So every afternoon, a couple hours before Sundance’s daily

injection, Pendergrass-Nethery and her husband give him a dose of gabapentin. When the time comes, they burrito him up into a white towel—"like a mummy," she said—and inject him with GS-441524. It's definitely a two-person job.

In the meantime, FIP Warriors has grown prominent enough that Chinese sellers are now approaching the group to market their GS-441524. They seem to pop up and then disappear. "It's hard to say if they're companies or sort of backdoor dealers," Kintz says. But the group has tried to institute a small measure of accountability. It had, at one point, tested a few popular brands to verify the concentration and content of their GS-441524 vials. When new sellers approach, the group asks for samples to send to cat rescues, which might not be able to afford GS-441524 for kittens that would otherwise certainly die of FIP. "That's generally how we determine if it works and if it's going to be okay," Kintz says. But the group is also rife with disclaimers about not being able to verify any particular drug.

Case in point: This January, a popular brand of GS-441524 appeared to kill cats that had been given the drug. When the group started noticing a pattern, admins began collecting data and warning against the brand's most recent batch. The man who had been selling it online disappeared, with several members of the group posting that he still owes them money. Rumor was that he and his wife had divorced acrimoniously; she had been the brains behind the operation and he had tried and failed to continue the business. Then a new brand of GS-441524 popped up—reportedly made by his wife. It's all impossible to verify half a globe away. "It's truly like the Wild West," Kintz says.

The recent surge of interest in remdesivir could change some of this dynamic. After Ebola trials found little benefit, remdesivir became a drug in search of a (human) disease. Should remdesivir ever be granted proper FDA approval beyond emergency use for COVID-19, and if it becomes common enough to prescribe through pharmacies, then vets could legally use it extra-label in cats. "It may be five years down the road, and COVID is a distant memory, and then it is used for FIP," Weigner says. For now, at least, the cat-specific data on remdesivir is still lacking.

Kintz hopes that GS-441524 can, one day, be legally available for cats. Then, she says, "no one would need me anymore, but that's okay."

https://bit.ly/2WjWsqs

The heat we fear may already be here

Heat and humidity beyond what the human body can tolerate is emerging ahead of projections, a new study suggests.

By Nick Carne

In a paper in the journal *Science Advances*, researchers present observational data showing that wet-bulb temperature – which incorporates measures of humidity – has in some places already exceeded 35 degrees Celsius, the point at which humans can no longer regulate body heat.

"Previous studies projected that this would happen several decades from now, but this shows it's happening right now," says lead author Colin Raymond from Columbia University, US, who worked with Columbia's Radley Horton and Tom Matthews from Loughborough University, UK.

As occurrences to date have tended to be brief and very localised, they have not been picked up by previous studies that looked at averages of heat and humidity measured over large areas and over several hours at a time, the researchers say.

For their study, they looked at hourly data from 7877 individual weather stations, allowing them to pinpoint shorter bouts affecting smaller areas.

Analysing data, they found that extreme heat/humidity combinations doubled between 1979 and 2017. Repeated incidents

appeared in much of India, Bangladesh and Pakistan; northwest Australia; and along the coasts of the Red Sea and Mexico's Gulf of California.

Incidents tended to cluster along confined seas, gulfs and straits, where evaporating seawater provides abundant moisture to be sucked up by hot air. However, moisture-laden monsoon winds or wide areas of crop irrigation appear to play the same role in some inland areas.

As *Cosmos* reported four years ago, humidity could genuinely be the killer in climate change because it worsens the effects of heat.

Humans cool their bodies by sweating; water expelled through the skin removes excess body heat, and when it evaporates, it carries that heat away. The process works nicely in deserts, but less well in humid regions, where the air is already too laden with moisture to take on much more.

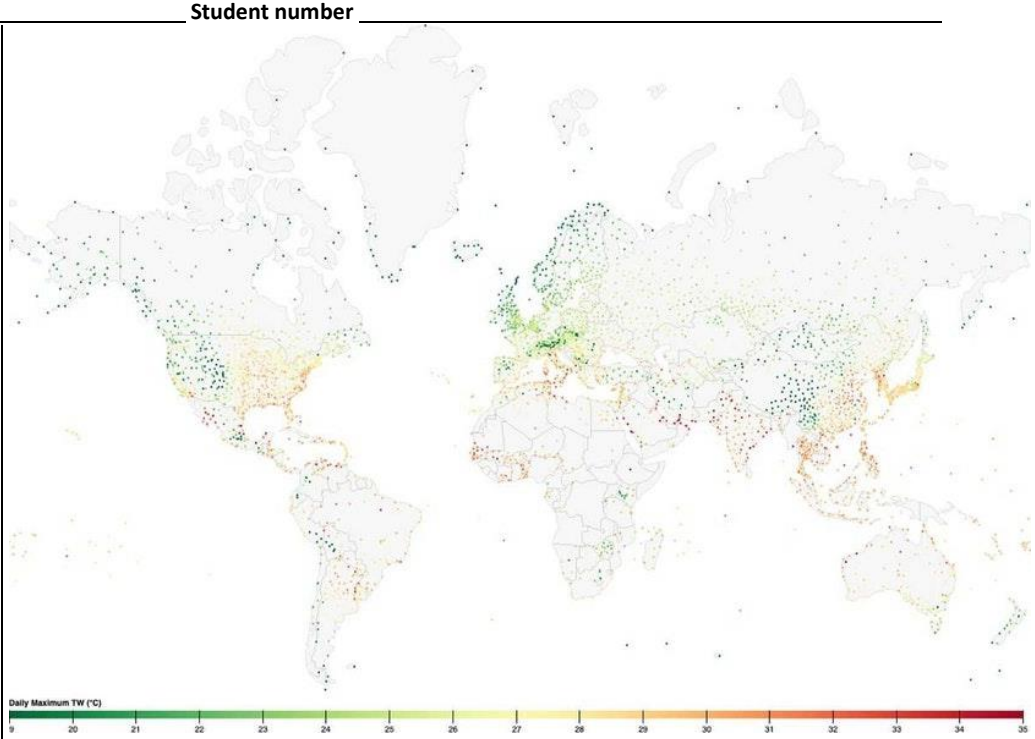
Raymond and colleagues say prior studies have suggested that even the strongest, best-adapted people cannot carry out normal outdoor activities when the wet-bulb hits 32 degrees Celsius (equivalent to a US heat index of 132 degrees Fahrenheit). A reading of 35 – the peak briefly reached in some Persian Gulf cities – is the theoretical survivability limit.

"It's hard to exaggerate the effects of anything that gets into the 30s," said Raymond.

The study found that worldwide, wet-bulb readings approaching or exceeding 30 on the wet bulb have doubled since 1979. There were about 1000 readings of 31 (previously believed to occur only rarely, the researchers say) and 80 of 33 (almost non-existent).

Kristina Dahl, a climatologist at the Union of Concerned Scientists, says some localities may already be seeing conditions worse than the study suggests, because weather stations do not necessarily pick up hot spots in dense city neighbourhoods

An interactive version of the map below is available here.



Documented instances of a potentially fatal mix of heat and humidity, with hotter colours (from yellow to red) signifying the worst instances. **Jeremy Hinsdale; adapted from Raymond et al., Science Advances, 2020**

https://bit.ly/3bcsP4L

Even if a successful coronavirus vaccine is developed, billions could struggle to access it because of a global shortage of glass vials

Business Insider spoke to four experts who warned that the vial supply chain is straining, and will affect the release of a coronavirus vaccine.

Bill Bostock

At this moment, more than 100 coronavirus vaccines are being developed at breakneck speed in labs around the world, with a handful eagerly awaiting early readouts from human trials.

But when a vaccine is approved — which looks to be September at the earliest — manufacturers will struggle to source enough glass vials to bottle enough for a global immunization drive, experts say.

If this happens, COVID-19 will continue to infect people around the world — even while a vaccine exists — because of delays not in science, but the manufacturing supply chain.

Vaccine vials are shaped from specialized glass — suppliers like ThermoFisher Scientific and Schott trademark their glassware — and tend to house between 2 ml and 100 ml of liquid. They measure, on average, 45 mm tall by 11.5 mm wide.

They have to withstand cold temperatures, and survive the wear and tear of being transported around the world.

The process of bottling vaccines is known in the industry as "fill-and-finish," and is invariably the main reason for vaccine delays.

It's an arduous process, where machines siphon fluid into millions of vials and syringes before each one is hand-checked for quality.

And to produce nearly 8 billion doses of a vaccine — one for each person in the world — is no mean feat, especially when there may not be enough vials for everyone.

"Quite clearly there will be a need to ramp up production of those vials," Professor Jeffrey Almond, a former vice president of research at Sanofi and current fellow at the University of Oxford's pathology department, told Business Insider.

"I'd be amazed if the people who are producing these things aren't already on it flat out, going at it all night long," he added.

Warnings pile up

In a whistleblower complaint publicly released Tuesday, Dr. Rick Bright — who was recently fired as the head of the US Biomedical Advanced Research and Development Authority (BARDA) — said he had warned the Department of Health and Human Services of a "critical shortage" of glass vials.

"It could take up to two years to produce enough vials for US vaccine needs," Bright said, according to the complaint.

And on April 30, Sir John Bell, Regius Professor of Medicine at the University of Oxford, told the BBC's "Today" radio program: "There's only 200 million vials left in the world now because they've all been sucked up by various people who can anticipate a vaccine."

Bell works with the Oxford Vaccine Group, whose vaccine is currently undergoing human trials.

The director of the UK's Wellcome Trust, Sir Jeremy Farrar, also told Channel 4 News this week: "There's apparently a glass shortage at the moment. So if the vaccine has to be put into glass vials, we need to make sure we have that available."

And Bill Gates, whose foundation has poured hundreds of millions of dollars into coronavirus vaccine research, told "The Ezra Klein Show" in late April: "Even the bottles, the fill-finish... the world doesn't have enough of that."

Other vaccine development groups include pharmaceuticals company Janssen, a division of Johnson & Johnson, which told Business Insider it plans to "provide a global supply of more than one billion vaccine doses." It hopes to fit five doses in a single vial to save glass, The New York Times reported.

J&J has declined to say how many glass vials it had access to. But James Robinson, vice president of the Coalition for Epidemic Preparedness Innovations (CEPI), told FiveThirtyEight last month Janssen had preordered 250 million vials.

"That might be all that's out there," Robinson said, adding that CEPI — which finances vaccine research — is hurrying to source 200 million vials itself.

The vial shortage could hold up a global vaccine release

It's not clear how many glass vials exist in the world, because there is no central authority.

In the US, vaccine makers are obligated to notify the the Food and Drug Administration (FDA) about any material shortages.

However, the FDA told Business Insider that "manufacturers of glass vials are not."

Meanwhile, the UK Vaccine Network, a government-mandated expert group, has warned that fill-and-finish is often the cause of delays in the production of vaccines.

"Identifying a suitable fill finish site could be a bottleneck that adds delays to the manufacturing process," it has said. "Finding a suitable production slot within the site's production calendar can also become limiting."

Vijay Samant, former head of vaccine manufacturing at Merck, told The New York Times: "The manufacturing task is insurmountable. I get sleepless nights thinking about it."

Business Insider asked the big-four vaccine manufacturers — GlaxoSmithKline, Merck, Sanofi, and Pfizer — to outline their supplies of glass vials. The quartet are responsible for around 90% of all the world's vaccines.

GSK told Business Insider: "We continue to work closely with suppliers, including of glass vials, in respect of current and future needs."

Merck, Sanofi, and Pfizer did not respond to requests for comment.

'The critical weak link in this whole supply chain'

Glass vials are extremely hard and time-consuming to make.

"They take months to manufacture and the world has only created a capacity for what it uses for everyday treatments, so there is no surge capacity," Marc Koska, the inventor of a self-destructing syringe that helped reduce HIV transmission, told watch company Bremont, for which he is an ambassador.

"If we went to China now, or indeed anywhere in the world, to ask for a billion glass vials to inject everyone in Europe twice, it would be many months or years before we got supply. That has become the critical weak link in this whole supply chain."

Vial makers will have to work relentlessly to boost production, said Prashant Yadav, a healthcare supply chain expert at the Center for Global Development.

"For workers on the fill-and-finish line, companies will have to incentive all these peoples to work their lives the same way as the scientists, 20 hours a day to make more vials and increase capacity," he told Business Insider.

How often and how much people need to get vaccinated will also affect supply chains

Whether the vaccine is bottled in multi-dose vials, which can house from two to 20 doses, or single-use vials — which house just one dose — will impact vial stocks too.

Multi-dose vials are more economical than single-use vials in terms of glass per dose and other production costs. But singles are necessary for pharmacies and drugstores to vaccinate people who miss an initial mass vaccination drive.

"Logically, you're going to put it in multi-dose vials. Getting into individual syringes is a hell of a job, much slower, [and] would put huge demand on pack-and-fill facilities," Almond told Business Insider.

Dose sizes will also affect the demand for vials.

Yadav, the supply chain expert, told Business Insider: "The extent of the shortage will depend on what type of vaccine comes out, as multi-dose vials will mean less of an issue."

"But, if you open a vial, and you don't have enough patients, that vaccine is wasted."

He added of efforts to address the shortage: "We don't know if vial makers, which is a concentrated market, have received clear signals of what to expect from distributors."

Single- vs double-dose?

Another key factor distributors need to consider is the fact that people may need to vaccinate themselves more than once to boost their immunity against COVID-19.

"It's also likely that annual boosters may be needed," Robin Shatlock, head of Mucosal Infection and Immunity at Imperial College London, told Business Insider.

Almond, the former Sanofi VP, said it's more likely that a double-dose vaccine — two smaller doses taken separately — will be needed, which means using more glass per dose.

"Be prepared on the two-shot route to risk even more shortages," he said. "The probability is that it is going to be significantly better with two doses than one. If you have a dose and then another dose, say, two months later, you boost your response."

It's not yet clear whether a single- or double-dose coronavirus vaccine will best immunize people against COVID-19. Labs that are doing human trials, like Pfizer and the Oxford Vaccine Group, are still expecting early results.

Dr Paul F. McKay, a senior infectious-diseases researcher at Imperial College London, told Business Insider: "My personal opinion is to get as many doses to the public as quickly as possible, and if that requires multi-dose vials, then that's what we should do."

Glass vials are still needed to produce vaccines for other diseases

While the coronavirus is indisputably the most pressing heath issue in the world, the constant supply of other key vaccines — like meningitis, influenza, and typhoid — must be maintained.

"The vaccines industry is used to producing hundreds of millions of doses of flu vaccines every year, and hundreds of millions of other vaccines," Almond told Business Insider.

"The materials and the facilities are there but, of course, you don't want to distort things by stopping doing all those things. Otherwise you're going to have to a whole load of deaths in kids who don't get the proper vaccines."

The current outbreak of "COVID-19 on top of all that creates some logistical issues and probably some supply problems as well," he said.

Cardinal Health, a US vial manufacturer, also told The New York Times that the pandemic is creating supply-chain issues like "delays in inventory replenishment for certain products."

GAVI, the vaccine alliance, told Business Insider it is "working with partners" to ensure a vaccine "can be made available to countries as soon as possible," but did not comment on global levels of vials.

The Oxford Vaccine Group declined to comment on distribution and manufacturing.

https://wb.md/2SR9sbc

COVID-19 Dermatologic Manifestations: More Than Just a Footprint

Skin manifestations of SARS-CoV-2 weren't recognized at early stages of the pandemic, but have received much recent attention in scientific journals.

Graeme M. Lipper, MD

The skin manifestations of the novel coronavirus SARS-CoV-2 were not recognized at the early stages of the pandemic but have received much recent attention in scientific journals and global media outlets. Reported manifestations range from pseudo-chilblains to a morbilliform (measles-like) exanthem, urticaria, vesicular eruptions, a dengue-like petechial rash and ovate scaling macules, and plaques mimicking pityriasis rosea.

The New 'Great Mimicker'

Much like with HIV and syphilis, COVID-associated "rashes" seem to be as numerous as they are hard to pin down. The largest published study to date is a nationwide case series in Spain with

375 cases which identified five clinical patterns. Because of the scarcity and low sensitivity of diagnostic tests available, the investigators accepted patients with confirmed disease as well as those with a clinical diagnosis of COVID in the study. Just under half (41%) of patients with pseudo-chilblains had confirmed infection with positive viral cultures and/or serology.

Observed COVID-associated skin patterns were:

- ***Acral erythema with vesicles or pustules; so-called "pseudo-chilblains" (19%)***
- ***Vesicular (chicken pox-like) eruptions (9%)***
- ***Maculopapular eruptions (47%)***
- ***Urticaria (19%)***
- ***Livedo or necrosis (6%)***

These investigators found that the vesicular eruptions appeared earliest in the course of COVID-19, prior to any other symptoms in 15% of cases; these developed on the trunk and extremities, were most common in middle-aged adults, and typically lasted around 10 days.

In contrast, the pseudo-chilblains eruption which has received much attention on social media (using the hashtag #COVIDtoes) occurred later. In almost two thirds (59%) of patients, these lesions developed after other symptoms. Despite much concern in the lay press about lesions on toes (which can also, less frequently, present on fingers), pseudo-chilblains acral lesions correlated with a milder disease course and younger patient age. Livedo and necrosis, however, indicated more severe illness and a poor prognosis.

Patients with maculopapular exanthems (47% of reported cases in this series) also had more severe infections and typically manifested skin findings at the same time as other COVID-19 symptoms.

Sounding the Alarm in Kids

In a recent and alarming twist, more than a dozen children—the group once thought to be most immune to severe COVID complications—have presented in the United Kingdom with a multisystem inflammatory condition with features of toxic shock syndrome and atypical Kawasaki disease. Kawasaki-like signs of this "SARS-CoV-2-related inflammatory syndrome" include an erythematous rash, conjunctivitis and glossitis with high fever, abdominal pain and gastrointestinal symptoms, and cardiac inflammation. Another 25 children with similar findings have been identified in France.

Some of these children have tested SARS-CoV-2 positive or had serologic evidence of prior SARS-CoV-2 infection. These findings prompted a warning from the National Health Service and the Paediatric Intensive Care Society.

A similar alert was just issued by the New York City Health Department after 15 children, ages 2-15, were hospitalized in NYC between April 17 and May 1 with illnesses compatible with this syndrome (ie, typical Kawasaki disease, incomplete Kawasaki disease, and/or shock). Polymerase chain reaction (PCR) testing for SARS-CoV-2 was positive in four of the NY children. As of May 6, 2020, the reported number of children affected in New York had risen to 64 and cases in other states were reported.

COVID Toes

Of all the COVID-associated skin manifestations, pseudo-chilblains has drawn the most attention to date. "COVID toes" were first described in China and then in Europe by a network of dermatologists in Italy, Spain, Belgium, and France. These cases typically affect children and young adults, manifesting as acro-located erythematous to violaceous papules and plaques primarily affecting the toes and mimicking chilblains (idiopathic pernio).

Classic cold-induced chilblains is a benign and self-limited condition characterized by acral erythema of the toes (and sometimes fingers) with swelling. In contrast, pseudo-chilblains (COVID toes) often occurs in warmer climates, tends to be more

severe and symptomatic (itching, burning, pain), is more likely to ulcerate, and takes longer to resolve.

The earliest case series describing "acro-ischemia presentations" included finger and toe cyanosis, skin bullae, and dry gangrene. This Chinese case series looked at seven critically ill patients with COVID-19 pneumonia, diagnosed and treated in Wuhan in early February. In addition to having fever, cough, and dyspnea, all of the patients developed finger and/or toe cyanosis which progressed to bullae, skin ulceration, and necrosis. All of these individuals also had evidence of a hypercoagulable state with elevated D-dimers and fibrinogen degradation products, and prolonged prothrombin times. Despite treatment with low-molecular-weight heparin, these patients had a poor prognosis; five died with a median time from acro-ischemia onset to death of 12 days.

In contrast, the reported cases of pseudo-chilblains coming out of Europe, the Middle East, and the United States fit more into the benign pattern described by researchers in Spain.

A recent paper described a case involving a 23-year-old man. He presented with sudden-onset "violaceous, infiltrated, and painful plaques on the toes and lateral aspect of the feet," preceded by fever and a dry cough. This patient had no prior history of chilblains, Raynaud's phenomenon, or collagen vascular disease. A nasopharyngeal swab tested PCR-positive for SARS-CoV-2, and coagulation studies were normal with no D-dimers. Histopathology was similar to that of idiopathic pernio, showing a small-vessel lymphocytic vasculitis with variable levels of papillary dermal edema and no intravascular thrombi.

Anecdotally, most young patients with pseudo-chilblains seem to follow this benign course, often remaining otherwise asymptomatic. Adding to the uncertainty, some with clinical features and a history highly suggestive of COVID-related pseudo-chilblains have tested SARS-CoV-2-negative by PCR and/or serologies.

Discussion

The story of COVID-19 and skin manifestations is changing every day, with dozens of papers still in press. While the spotlight has fallen on pseudo-chilblains ("COVID toes"), the pathophysiology behind this strange manifestation remains mysterious. Some question whether this is a true COVID manifestation or merely an epiphenomenon—so-called "quarantine toes"—brought about by more people walking barefoot during quarantine and an unusually cold spring in parts of the United States.

Some cases may indeed be idiopathic pernio, which is more likely to be reported due to detection bias, given the large amount of recent media coverage about this finding.

Neither detection bias nor a cold spring in the United States can explain the fact that cases are occurring in warm climates in individuals with positive SARS-CoV-2 viral swabs or serologies. A second unrelated infectious trigger causing a surge in pernio, while possible, seems far-fetched.

COVID-associated pernio is treated with the same drugs used for idiopathic pernio. These include high-potency corticosteroids, aspirin, topical calcium channel blockers such as nifedipine, and nitroglycerin paste. All of these uses are off-label.

Decisions in patients with COVID-related skin manifestations plus other characteristic symptoms (eg, cough, fever, shortness of breath, anosmia, loss of taste) or known COVID exposure are easy. They should be tested via nasopharyngeal swab and serologies.

In contrast, those with suspicious skin manifestations who are otherwise asymptomatic, especially with no other risk factors, fall into a gray area. Should such individuals be tested? Should they self-quarantine? To date, there is no clear consensus.

Thanks to coordinated efforts such as the nationwide consensus study in Spain and the American Academy of Dermatology's COVID-19 Dermatology Registry, we can anticipate a better

understanding of how and why SARS-CoV-2 affects the skin. Hopefully, these insights will shed light on why this pathogen is so deadly for some and yet mild or asymptomatic in others.

Graeme M. Lipper, MD, is a clinical assistant professor at the University of Vermont Medical College in Burlington, Vermont, and a partner at Advanced DermCare in Danbury, Connecticut.

https://bit.ly/2SSMqcJ

Men's blood contains greater concentrations of enzyme that helps COVID-19 infect cells

Finding may explain why men with heart failure suffer more from the coronavirus than women

Evidence from a large study of several thousand patients shows that men have higher concentrations of angiotensin-converting enzyme 2 (ACE2) in their blood than women. Since ACE2 enables the coronavirus to infect healthy cells, this may help to explain why men are more vulnerable to COVID-19 than women.

The study, published in the *European Heart Journal* [1] today (Monday), also found that heart failure patients taking drugs targeting the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), did not have higher concentrations of ACE2 in their blood.

Dr Adriaan Voors (MD-PhD), Professor of Cardiology at the University Medical Center Groningen (The Netherlands), who led the study, said: "Our findings do not support the discontinuation of these drugs in COVID-19 patients as has been suggested by earlier reports."

Some recent research suggested that RAAS inhibitors might increase concentrations of ACE2 in plasma - the liquid part of blood - thereby increasing the risk of COVID-19 for cardiovascular patients taking these drugs. The current study indicates that this is not the case, although it looked only at ACE2 concentrations in plasma, not in tissues such as lung tissue. In addition, the study cannot provide definitive evidence on the effects of RAAS inhibitors in patients with COVID-19. Its conclusions are mainly restricted to heart failure patients, and the patients did not have COVID-19, so the researchers cannot provide a direct link between the course of the disease and ACE2 plasma concentrations.

Prof Voors said: "ACE2 is a receptor on the surface of cells. It binds to the coronavirus and allows it to enter and infect healthy cells after it is has been modified by another protein on the surface of the cell, called TMPRSS2. High levels of ACE2 are present in the lungs and, therefore, it is thought to play a crucial role in the progression of lung disorders related to COVID-19."

Prof Voors and his colleagues were already studying differences in markers of disease in the blood between men and women before the coronavirus outbreak. The results became available soon after the pandemic began.

The first author of the study, Dr Iziah Sama from UMC Groningen, said: "When we found that one of the strongest biomarkers, ACE2, was much higher in men than in women, I realised that this had the potential to explain why men were more likely to die from COVID-19 than women."

The researchers measured ACE2 concentrations in blood samples taken from two groups of heart failure patients from 11 European countries [2]. There were 1485 men and 537 women in the first group, the index cohort, which was designed to test the researchers' hypotheses and research questions. Then the researchers validated their findings in a second group of 1123 men and 575 women, the validation cohort.

The median (average) age of the participants in the index cohort was 69 years for men and 75 years for women, and in the validation cohort it was 74 and 76 years, respectively.

When the researchers looked at a number of clinical factors that could play a role in ACE2 concentrations, including the use of ACE inhibitors, ARBs and mineralocorticoid receptor antagonists (MRAs), as well as a history of chronic obstructive pulmonary disease, coronary artery by-pass graft and atrial fibrillation, they found that male sex was the strongest predictor of elevated ACE2 concentrations. In the index cohort, ACE inhibitors, ARBS and MRAs were not associated with greater ACE2 plasma concentrations, and in the validation cohort, ACE inhibitors and ARBs were associated with lower ACE2 concentrations, while MRAs were only weakly associated with higher concentrations.

"To the best of our knowledge, this is the first substantial study to examine the association between plasma ACE2 concentrations and the use of blockers of the renin-angiotensin-aldosterone system in patients with cardiovascular disease. We found no evidence that ACE inhibitors and ARBs were linked to increased ACE2 concentrations in plasma. In fact, they predicted lower concentrations of ACE2 in the validation cohort, although we did not see this in the index cohort," said Prof Voors.

"The effect of MRAs on ACE2 concentrations is not clear, as the weak increase in concentrations in the validation cohort was not seen in the index cohort. Our findings do not suggest that MRAs should be discontinued in heart failure patients who develop COVID-19. They are a very effective treatment for heart failure and the hypothetical effects on viral infection should be weighed carefully against their proven benefits," he said.

ACE2 is found not only in the lungs, but also the heart, kidneys and the tissues lining blood vessels, and there are particularly high levels in the testes. The researchers speculate that its regulation in the testes might partially explain higher ACE2 concentrations in men, and why men are more vulnerable to COVID-19.

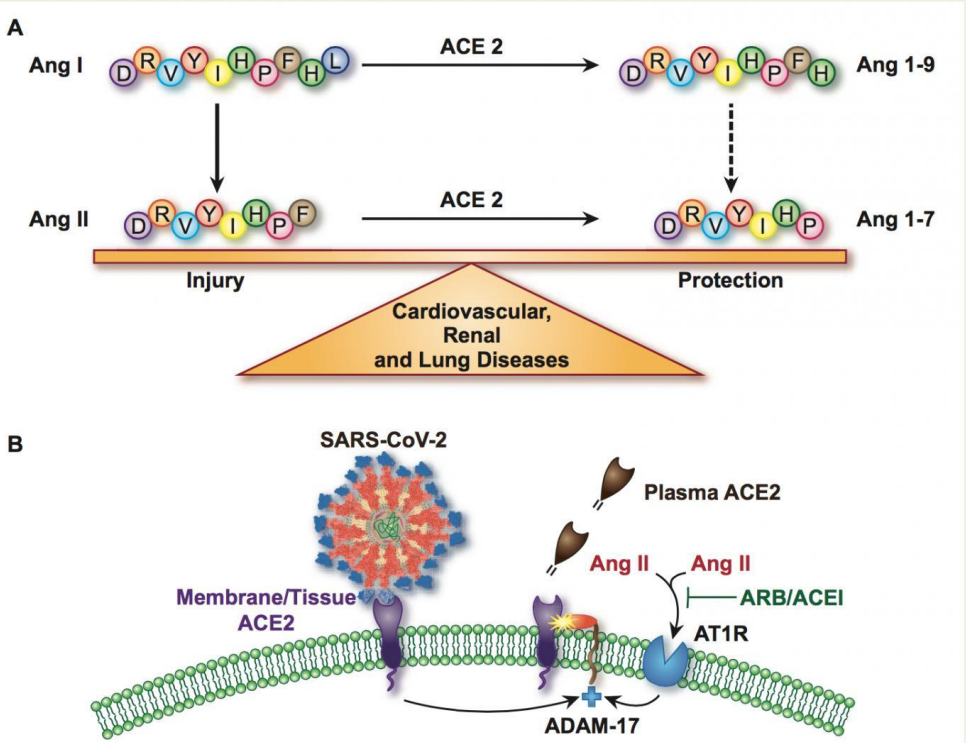


Figure 1 The role of ACE2 in controlling the renin–angiotensin system and the proteolytic shedding of membrane-bound ACE2 by ADAM-17. ACE2 converts Ang I and Ang II into Ang 1-9 and Ang 1-7, respectively, thereby negatively regulating the renin–angiotensin system (A). ACE2 serving as the receptor for the SARS-CoV-2 and activation of ADAM-17 by Ang II and SARS-CoV-2 binding leading to a loss of membrane-bound ACE2 attenuates a key homeostatic mechanism limiting Ang II effects in tissues, culminating in cardiovascular, renal, and lung diseases, key components of the heart failure syndrome (B). Higher plasma ACE2 levels were associated with male sex, history of atrial fibrillation, and coronary artery bypass graft, higher NYHA class, and heart rate; reduced ACE2 levels were associated with a history of chronic obstructive pulmonary diease, and higher left ventricular ejection fraction and systolic blood pressure (Sama *et al.*[9]). The dotted line indicates a putative role for ACE.

The role of ACE2 in controlling the renin-angiotensin system and the proteolytic shedding of membrane-bound ACE2 by ADAM-17. **European Heart Journal**

Other limitations of the study include the fact that the researchers only measured concentrations of ACE2 in plasma, not in tissues, so they cannot be sure that concentrations in the blood are similar to those seen in tissues; it is the ACE2 in the lung tissues that are thought to be important for viral infection of the lungs, not ACE2 concentrations in the blood.

In an accompanying editorial [3], Professor Gavin Oudit, from the University of Alberta, Canada, and Professor Marc Pfeffer, from Brigham and Women's Hospital, Harvard Medical School, USA, write: "When faced with the rapidly expanding COVID-19 pandemic and in the absence of definitive data, the results of Sama et al obtained in heart failure patients in the pre-COVID-19 period offer supporting evidence to continue ACE inhibitors or ARBs in patients at risk for SARS-CoV-2 infection. However, this field is moving so rapidly that we now have two observational studies of ARB/ACE inhibitor use in hospitalized COVID-19 patients showing no augmented risk to COVID-19 patients and even suggesting possible benefit."

The study is one of several research papers, clinical reviews, editorials and discussion papers on COVID-19 and cardiovascular disease to be published in a special issue of the *European Heart Journal* on Thursday 14 May. [4]

Notes:

[1] "Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors", by Iziah E. Sama et al. European Heart Journal. doi:10.1093/eurheartj/ehaa373

[2] The 11 European countries are: The Netherlands, UK, Germany, France, Greece, Slovenia, Serbia, Italy, Norway, Poland, Sweden.

[3] Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-19", by Gavin Y. Oudit and Marc A. Pfeffer. European Heart Journal. doi:10.1093/eurheartj/ehaa414

[4] ""Focus issue on COVID-19 and CVD," European Heart Journal, Issue 19. https://academic.oup.com/eurheartj/issue/41/19

https://bit.ly/3dKT3NN

A researcher behind one of the most accurate antibody tests available explains when you should get tested — and how to understand your results

Researchers at New York's Mount Sinai Hospital shared the results of their coronavirus antibody test this week.

Aria Bendix

Almost every patient in the study who tested positive for a coronavirus infection later tested positive for antibodies. That means false negatives are unlikely.

The hospital's director of clinical antibody testing said people should wait at least three weeks after their symptoms appear to get tested.

Patients who test positive likely have immunity to the virus, but questions linger about how long immunity will last.

As states and countries begin rolling back their lockdown restrictions, the results of widespread antibody testing may guide policies on whether schools can reopen or employees can return to work. But for some people who have received one of these tests, the results have yielded more questions than answers.

Not all coronavirus antibody tests are the same. A team of Bay Area researchers recently evaluated 14 on the market and found that only three were consistently reliable. Many of the tests produced false positives, meaning they signaled antibodies that a person didn't have.

Plus, the results can be skewed based on when a person gets tested over the course of their illness, according to Ania Wajnberg, the director of clinical antibody testing at Mount Sinai Hospital in New York.

Mount Sinai recently shared results from its own antibody testing project; the test was approved for clinical use by the US Food and Drug Administration in April. The findings showed that all but three of the 600-plus patients who had confirmed coronavirus cases tested positive for antibodies. Of more than 700 "suspected cases" — people who had coronavirus symptoms and lived with someone who tested positive or were told by a doctor that they likely had the virus — only 38% tested positive for antibodies.

"I think there's a lot of people that think maybe they had it who didn't," Wajnberg said.

Wajnberg offered advice about when to get tested and how to understand your results, based on her team's research.

Certain tests could provide a better indication of long-term immunity

Different tests screen for different antibodies. In Mount Sinai's case, the test looks for immunoglobulin G (IgG), the most common antibody found in blood and other body fluids. Other tests may screen for immunoglobulin M (IgM), which also circulates in the blood, or immunoglobulin A (IgA), an antibody found mainly in the respiratory and digestive tracts.

In general, our bodies make IgM first in response to a viral infection. IgM is also associated with more acute viral infections, whereas IgG develops over a longer period of time. That means IgG is usually a better indicator of long-term immunity, but coronavirus patients who get tested shortly after developing symptoms may not have produced these antibodies yet.

Scientists haven't determined if IgG antibodies confer immunity to this particular coronavirus, but the Mount Sinai researchers found that some level of protection is likely.

"Even though we don't know what's going on with this disease yet, if IgG confers immunity, that's the more important one that has implications for going back to work," Wajnberg said.

The Bay Area researchers found that IgM tests produced more variable results than IgG tests, but the most consistent results came from testing for both antibodies at once.

Wait 3 weeks to get an antibody test if you're sick

In the Mount Sinai study, 113 patients who were confirmed to have had the virus initially tested negative or "weakly positive" for antibodies; but when they were tested a second time, the majority tested positive for antibodies.

"In order to get the most meaningful results, the antibody tests are best if you wait a full three weeks after the start of your illness," Wajnberg said. "We even saw a small difference in our paper at 24 days versus 20 days."

Patients may even want to wait four weeks to be safe, she added, but they shouldn't worry that the antibodies will disappear if they wait too long. For other coronaviruses like SARS and MERS, IgG antibodies seemed to peak within months of an infection and last for a year or more.

"It is confusing for people because the viral tests are almost the opposite," Wajnberg said. "Those you want to do the minute you're not feeling well, because if you wait a month and you're feeling better, then the viral test might be negative."

Patients should be symptom-free for 2 weeks

Wajnberg recommended waiting two weeks after symptoms resolve to get an antibody test, though she said a patient who has been sick for a few weeks or more is likely to have developed antibodies by that point.

All patients involved in the Mount Sinai study were fully recovered — meaning they felt close to normal — by the time they received their antibody test.

"Not everybody was back to fully 100%, but I would say 90-plus," Wajnberg said.

Around 19% of the patients tested positive for an active infection after their symptoms resolved. Wajnberg said it's possible that those patients were still contagious, but the more likely scenario is that they were shedding dead virus.

"What we're finding on the swab is not infectious live virus — it's dead virus or fragments of virus or even virus eaten up by your immune system," she said.

According to Wajnberg, there's no reason to think that severe cases lead the body to produce more antibodies, since almost every patient in the Mount Sinai study had mild or moderate illnesses.

"In some viruses, the more severe you are, the higher antibodies you make. This study would suggest that that's not really the case," she said. "But we just don't know yet."

The researchers also found that the duration of symptoms didn't influence a person's antibody response. Instead, Wajnberg said, the amount of antibodies a person produces may be related to innate differences in people's immune responses.

Antibody tests could produce false negatives, but false positives are more likely

With any coronavirus antibody test, researchers establish a minimum threshold of antibodies that are required for the results to come back positive. Wajnberg said the Mount Sinai team set a relatively high threshold to prevent people from testing positive with a low antibody count — which could perhaps lead people to false assumptions that they had immunity to the virus.

"The lower you set a threshold, the more likely you are to have false positives," she said.

The study's results indicate that false negatives are very unlikely, though not impossible.

"With the numbers of people we're testing, even at a high sensitivity and specificity, you're still going to have false results — that's true of any test in the whole world," Wajnberg said.

Researchers also still don't know the specific levels of antibodies required for a person to be fully immune; even patients with a lower threshold might still be protected. But there's still a lot to learn, Wajnberg said.

"It's super frustrating for people when they feel sure that they had [the coronavirus] and then the tests are not bearing that out," she said. "This is a crazy situation where we almost want to test everyone on Earth because we know that the tests aren't perfect."