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COVID Breakthrough: New Potent Antiviral Against SARS-CoV-2, RSV and Other Respiratory RNA Viruses

Center for Translational Antiviral Research Reports Novel Drug Class with Activity Against SARS-CoV-2

The COVID-19 pandemic and resurgence of infections by other respiratory RNA viruses such as respiratory syncytial virus (RSV) in children has caused an urgent need for the development of orally available broad-spectrum antiviral therapeutics.

In a study published online on December 2, 2021, in *Science*, researchers in the Institute for Biomedical Sciences at Georgia State University report a new candidate ribonucleoside analog, 4'-fluorouridine (4'-FlU), that has potent antiviral activity against SARS-CoV-2, RSV and other respiratory RNA viruses in cell culture, human organoids and different animal models when administered orally once daily.

"Mechanistically, we show that 4'-FlU is in a different class from molnupiravir that is currently considered for regulatory approval," said Dr. Richard Plemper, Distinguished University Professor, director of the Center for Translational Antiviral Research at Georgia State and senior author of the study. "4'-FlU does not act as a mutagen but induces termination of the viral polymerase, aborting replication of the viral genome. There is an urgent need to expand the therapeutic arsenal against SARS-CoV-2 and 4'-FlU has strong developmental promise as a companion drug."

In the study, 4'-FlU was tested against different SARS-CoV-2 variants of concern in ferrets, which have emerged as a leading model for drug testing, and against respiratory syncytial virus in mice. The researchers found that this drug potently blocked SARS-CoV-2 replication, including the gamma and delta variants in the ferret, and efficiently suppressed RSV burden in mouse lungs.

"We are excited that 4'-FlU is the only orally available antiviral candidate currently developed against SARS-CoV-2 that is active when given once daily," said Dr. Julien Sourimant, first author of the study and a researcher in Dr. Plemper's lab in the Institute for Biomedical Sciences, "which should be a major asset in ensuring outpatient compliance."

Reference: "4'-Fluorouridine is an oral antiviral that blocks respiratory syncytial virus and SARS-CoV-2 replication" by Julien Sourimant, Carolin M. Lieber, Megha Aggarwal, Robert M. Cox, Josef D. Wolf, Jeong-Joong Yoon, Mart Toots, Chengin Ye, Zachary Sticher, Alexander A. Kolykhalov, Luis Martinez-Sobrido, Gregory R. Bluemling, Michael G. Natchus, George R. Painter and Richard K. Plemper, 2 December 2021, Science.
DOI: 10.1126/science.abj5508

This research on 4'-FlU emerged from a collaboration of the team at Georgia State University with researchers at Emory University and the Texas Biomedical Research Institute. The study was funded by public health service grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases to Georgia State University. Co-authors of the study include J. Sourimant, C.M. Lieber, M. Aggarwal, R.M. Cox, J.D. Wolf, J.-J. Yeong, M. Toots and R.K. Plemper at Georgia State University; C. Ye and L. Martinez-Sobrido at Texas Biomedical Research Institute; and Z. Sticher, A.A. Kolykhalov, G.R. Bluemling, M.G. Natchus and G.R. Painter at Emory University.

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Examining the neurotoxin from a black widow

The exact structure of the nerve poison was previously unclear

Phobias are often irrational by nature—especially in the case of spiders, as these creatures are usually more afraid of humans than vice-versa. But: some species are a force to be reckoned with—for example, the Latrodectus spider, more commonly known as the Black Widow. It catches its prey by using venom—to be precise, latrotoxins (LaTXs), a subclass of neurotoxins, or nerve poisons. A bite from a Black Widow can be fatal for humans. The exact structure of the nerve poison was previously unclear, but Prof. Christos Gatsogiannis from the Institute of Medical Physics and Biophysics at Münster University investigated the substance—not only because of its uniqueness, but also with a view to possible

medical applications. Using cryo-EM, and in collaboration with Gatsogiannis' former colleagues at the Max Planck Institute in Dortmund and with researchers at Jacobs University Bremen, the team of Münster researchers succeeded in explaining the first structure of a latrotoxin. The team's findings have now been published in the *Nature Communications* journal.

Neurotoxins are probably known to many non-specialists—in the form of botox, which is often used in cosmetic surgery. The Black Widow's poison, however, has anything but a "beautifying" effect: LaTX was developed by nature primarily in order to immobilize insects—or simply kill them straight off. In the process, the toxins dock onto specific receptors on the surface of nerve cells and cause neurotransmitters to be released, for example through a calcium channel. As a result of the constant inflow of calcium ions into the cell, transmitters are given off which lead to seizures.

This mechanism is what distinguishes the latrotoxins from all other variants of the so-called pore-forming toxins. "Despite wide-ranging studies carried out over many years, we didn't know the structure of these toxins," says Gatsogiannis. "For this reason weren't able to understand the precise active mechanism." Help was provided in the form of cryo-electron microscopy, or cryo-EM for short. By means of this three-dimensional method, biomolecules can now be "photographed" down to atomic resolution. In the process, the protein complexes in liquid ethane are frozen at minus 196 degrees, in milliseconds, into a thin layer of amorphous ice, a form of solid water. Hundreds and thousands of images are then captured which show different views of the proteins and, in this way, enable the structure of the neurotoxin to be recognized.

Using cryo-EM, and in collaboration with researchers at the Max Planck Institute in Dortmund and at Jacobs University Bremen, the team of Münster researchers succeeded in explaining the first structure of a latrotoxin. "The general structure of LaTX is unique and is different in every possible way from all other known toxins," says Gatsogiannis. The new insights are fundamental for understanding the molecular mechanism of the LaTX family, and they pave the way for possible medical applications—as well as for the development of an efficient antidote. In addition, these insights into insect-specific toxins might open up new opportunities for pesticides. For future research, however, it is essential to understand how exactly the toxin is inserted into the membrane, i.e. into the surface of the cell. "At the moment we are studying the structure of all members of the latrotoxin family—in particular how they exactly recognize the specific receptors on the surface of the cell, and how these sensors function," Gatsogiannis explains.

The biggest obstacle to these plans is the fact that cryo-EM is not yet available in the Münster area. Prof. Gatsogiannis and his team want to change this: "The practical importance for medical research is immense," says Dr. Minghao Chen, the lead author of the study now published, "as 'function' is directly linked to 'structure' in a biological context. But the method is highly complex and requires an ultramodern infrastructure." The research team plans to introduce this innovative method soon in Münster University's new research building, the Center for Soft Nanoscience (SoN).

More information: *Minghao Chen et al, Molecular architecture of black widow spider neurotoxins, Nature Communications (2021).* *DOI: 10.1038/s41467-021-26562-8*

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Seaweed Extract Stops COVID in Early Testing

Experiments suggest that ulvan, an extract from ulva, or "sea lettuce," may help fight COVID-19

Lisa Rapaport

A type of marine algae known as ulva, or "sea lettuce," that's a diet staple in places like Japan, New Zealand, and Hawaii may have another benefit for people. Lab experiments suggest that ulvan, an extract from this type of algae, may help fight COVID-19.

Other forms of edible seaweed have also shown promise as antivirals against COVID -- at least in very early studies done in test tubes and animals. But ulvan has been tested as an antiviral treatment against certain agricultural and human viruses, too. This caused researchers to wonder whether ulvan might help prevent COVID infections.

To find out, scientists grew ulva algae in a lab, extracted ulvan, and then exposed cells in test tubes to both the coronavirus and to ulvan. When cells were exposed to ulvan, they didn't get infected with the coronavirus, according to experiment results reported in *PeerJ*.

In Test Tubes

That said, it's possible that the process used to extract ulvan from seaweed may impact its antiviral properties.

Investigators compared two extraction methods and found one of them resulted in ulvan with more than 10 times the virus-fighting power. This suggests that more research is needed to refine the best method to develop ulvan with the best antiviral properties, the researchers point out.

One limit of the experiment is that differences in the chemical makeup of the two extracts might have influenced the outcome, making it hard to know for sure how much of the antiviral activity might come directly from ulvan as opposed to these chemicals.

And even if the seaweed extract proves effective in more lab tests, it would still need to be tested in animals and humans. But should it prove effective in human trials, seaweed extract has the potential to help prevent COVID infection in people who can't easily afford or access vaccines, particularly in low-income countries, the study authors conclude.

Source

PeerJ: "Fighting SARS-CoV-2 with green seaweed Ulva sp. extract: extraction protocol predetermines crude ulvan extract anti-SARS-CoV-2 inhibition properties in in vitro Vero-E6 cells assay."

https://bit.ly/31S9ZAX

Giant Study Finds Viagra Is Linked to Almost 70% Lower Risk of Alzheimer's

New research suggests Viagra associated with dramatically reduced incidence of Alzheimer's disease

Peter Dockrill

Usage of the medication sildenafil – better known to most as the brand-name drug Viagra – is associated with dramatically reduced incidence of Alzheimer's disease, new research suggests.

According to a study led by researchers at the Cleveland Clinic, taking sildenafil is tied to a nearly 70 percent lower risk of developing Alzheimer's compared to non-users.

That's based on an analysis of health insurance claim data from over 7.2 million people, in which records showed that claimants who took the medication were much less likely to develop Alzheimer's over the next six years of follow up, compared to matched control patients who didn't use sildenafil.

It's important to note that observed associations like this – even on a huge scale – are not the same as proof of a causative effect. For example, it's possible that the people in the cohort who took sildenafil might have something else to thank for their improved chances of not developing Alzheimer's.

Nonetheless, the researchers say the correlation shown here – in addition to other indicators in the study – is enough to identify sildenafil as a promising candidate drug for Alzheimer's disease, the viability of which can be explored in future randomized clinical trials designed to test whether causality does indeed exist.

"Notably, we found that sildenafil use reduced the likelihood of Alzheimer's in individuals with coronary artery disease, hypertension, and type 2 diabetes, all of which are comorbidities significantly associated with risk of the disease, as well as in those without," explains computational biologist and senior author of the

study, Feixiong Cheng from the Cleveland Clinic.

It's not the first time sildenafil use has been linked with better health outcomes, with the drug previously showing promise in a range of different scientific contexts, including cancer and malaria research among others.

Here, Cheng's team began by building over a dozen endophenotype modules, using computational techniques to map genetic factors that could hypothetically govern the manifestation of Alzheimer's disease. With 13 of these modules in hand, the researchers then looked at what kinds of FDA-approved drugs might hypothetically help against the identified phenotypes.

Out of over 1,600 such medications already approved by the FDA, sildenafil turned out to be one of the most promising candidates.

That might sound baffling – given the drug is so far used in the main only for treating erectile dysfunction and pulmonary hypertension – in the research community, there were already signs the sildenafil compound might have other kinds of health benefits, given its interactions with the amyloid and tau proteins implicated in Alzheimer's pathology.

"Recent studies show that the interplay between amyloid and tau is a greater contributor to Alzheimer's than either by itself," Cheng says. "We hypothesized that drugs targeting the molecular network intersection of amyloid and tau endophenotypes should have the greatest potential for success… Sildenafil, which has been shown to significantly improve cognition and memory in preclinical models, presented as the best drug candidate."

The hypothesis appears to be borne out by the health insurance data, with the team finding sildenafil users had a 69 percent reduced risk of Alzheimer's disease compared to non-users – a reduction that was notably stronger than other kinds of medications also investigated in the study, including losartan, metformin, diltiazem, and glimepiride.

Of course, the researchers emphasize that none of this establishes causality, but on that front there may be other promising leads.

In separate experiments studying human brain cells in vitro to explore how sildenafil *might* confer protection against Alzheimer's cognitive decline, the researchers observed that neurons treated with the drug showed elevated growth and reduced tau accumulation.

It's early days, but those effects could well have something to do with the reduced chances of developing Alzheimer's in the insurance cohort. To that end, it's important to follow these leads further, the team says.

"We are now planning a mechanistic trial and a phase II randomized clinical trial to test causality and confirm sildenafil's clinical benefits for Alzheimer's patients," Cheng says. "We also foresee our approach being applied to other neurodegenerative diseases, including Parkinson's disease and amyotrophic lateral sclerosis, to accelerate the drug discovery process."

The findings are reported in *Nature Aging*.

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How bad is Omicron? Some clues are emerging, and they're not encouraging

New variant appears to evade immunity and shows signs of being more transmissible

By Kai Kupferschmidt, Gretchen Vogel

Testing stations and hospital wards in Gauteng, South Africa's most populous province. A company's Christmas party in Oslo, Norway, that became a superspreading event. Infection patterns in the United Kingdom.

Scientists are scouring patchy evidence from around the world to better understand Omicron, the new SARS-CoV-2 variant, and what it might mean for the next phase of the pandemic. Three weeks after Omicron was discovered, there are still mostly

questions, but a few hints have emerged—some worrisome, others more encouraging.

Researchers are focusing on three key questions: Can Omicron evade immunity from vaccines or previous infections? How transmissible is it? And how much severe disease will it cause?

The most solid clues so far pertain to the first question—and they are not reassuring. The genome alone—with more than 30 mutations in the all-important spike protein—suggested the variant might well be the best yet at dodging our immune defenses. And early data from South Africa seem to confirm that worry: A study posted as a preprint last week that analyzed 35,670 reinfections among nearly 2.8 million positive tests carried out through late November suggested an earlier infection with COVID-19 only offers half as much protection against the new variant as it does against Delta. That's a sign Omicron is able to escape at least some of the immune system's defenses, and it suggests COVID-19 vaccines may be less effective against the new variant as well. How big a problem that will become depends on whether vaccinations and previous infections still protect against severe disease, says Justin Lessler, an epidemiologist at the University of North Carolina. Chapel Hill.

Whether Omicron is more transmissible than its predecessors—as both Alpha and Delta were—is harder to judge. Omicron cases in South Africa have risen steeply in the past few weeks, but that could be explained in part by chance or the variant's ability to infect those who are vaccinated or had a previous infection.

But Jeremy Farrar, head of the Wellcome Trust, sees cause for concern. "The evidence that this is more transmissible is getting stronger every day," he says. In the United Kingdom, the number of positive polymerase chain reaction tests in which the gene encoding the spike protein cannot be detected (a sign of a likely Omicron infection) is increasing rapidly. In Oslo, a company Christmas party at a restaurant became a superspreading event, with at least 120 people testing positive; 19 cases so far have been confirmed as Omicron. (All attendees were vaccinated and had tested negative before the event.) In Denmark, 53 of 150 high school students who attended a party went on to test positive for Omicron.

"None of this alone tells us that this is more transmissible," says Kristian Andersen, an infectious disease researcher at Scripps Research. Superspreading events, for instance, have been a hallmark of SARS-CoV-2 from the start. "But Omicron is really rare still, so the fact that we see early cases being associated with superspreading events is quite concerning," Andersen says.

Early signs that Omicron causes less severe symptoms than previous variants offer some reassurance. Doctors in South Africa are reportedly seeing a larger proportion of mild COVID-19 cases in the hospital than at the start of earlier waves. The number of hospital patients infected with SARS-CoV-2 has been rising rapidly, but that includes "incidental" cases—patients seeking care for other reasons who test positive for the virus as well. Data through 6 December indicate the number who needed oxygen support was lower than in previous waves, suggesting fewer patients are suffering the serious lung damage from COVID-19 that has put so many in the hospital during the pandemic.

But it's too early to tell whether Omicron is really more benign. Many early cases in South Africa have been linked to a university outbreak and occurred in young people, who are less susceptible to severe disease. Previous infections could also be providing some protection, as could the steadily climbing vaccination rate in South Africa. Or it might simply be too early to see many serious cases, which can take weeks to develop and always make up a small proportion of the total number. "I haven't seen anything yet that tells me whether this is as severe or less severe, or more severe," Farrar says. "At the moment, my working assumption is that the

clinical syndrome of illness is the same as previous variants."

If that assumption holds, but the virus spreads more rapidly than Delta, more people would get severely sick in a short time period, which could mean a huge extra burden on health care systems that are already stretched thin—especially in places with low vaccine uptake and low levels of infection-induced immunity.

Even if Omicron causes milder disease, rapid spread could still quickly overwhelm hospitals in many places. "A small percentage of a large number is still a large number," says genomicist Mads Albertsen of Aalborg University, who serves on a panel advising the Danish government on SARS-CoV-2 variants. And it's not just about deaths and hospitalizations, says Mary Bushman, an epidemiologist at Harvard. "Part of what we need to think about is whether it's causing Long Covid," Bushman says.

More data from countries with different vaccination patterns will soon give a better picture of the threat Omicron poses. Scientists are particularly interested to see whether people who have had a booster shot are better protected.

In the meantime countries are scrambling to slow the variant's spread, with few signs of success. Bans against travelers from southern Africa are quickly losing their justification now that the virus seems entrenched in dozens of countries. Denmark, which has identified 183 Omicron cases so far, is trying to contain spread by broadening quarantine rules—asking not just people infected with the new variant and their close contacts to isolate, but also the close contacts of close contacts. But the rapid spread already makes that strategy impractical, Albertsen says.

That means it's down to the standard defenses such as wearing masks, social distancing, vaccination, testing, and isolation for those who test positive. "It's doing the basics well that matters, whatever the variant is called," Farrar says. Maria Van Kerkhove, an epidemiologist at the World Health Organization, says countries should pay extra attention to getting all of their vulnerable people fully vaccinated, including the elderly and those with conditions that can worsen COVID-19. "These are the people that governments should be targeting right now," she says.

Van Kerkhove is exasperated that with Omicron on their doorstep, many countries in the Northern Hemisphere haven't done enough to control big winter outbreaks of Delta. "We're not even out of the middle of this pandemic yet," she says, "and we're moving in the wrong direction."

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https://bit.ly/3IDKqV9

Natural Killer T Cells: In Breast Cancer, the Best Defense Is a Strong Offense

After pregnancy, breast cells call in specialized immune cells called Natural Killer T cells to prevent tumors from arising

Your immune system is constantly patrolling your body to keep you healthy. Sometimes, immune cells are also called into action to address a potential problem. Cold Spring Harbor Laboratory (CSHL) Associate Professor Camila dos Santos' lab discovered that after pregnancy, breast cells call in immune system reinforcements called Natural Killer T (NKT) cells to prevent tumors from arising. This finding illuminates a new way in which pregnancy reduces the risk of breast cancer.

In the immune system, there are two lines of defense. The first is the innate response, which involves immune cells that attack any foreign molecule they encounter. The second is the adaptive response, which consists of immune cells that respond specifically to calls for help from certain molecules. NKT cells are a unique population of cells that are present throughout the body and that can participate in both responses. CSHL graduate student Amritha Varshini Hanasoge Somasundara says that in post-pregnancy:

"There is an increase in this specific [NKT] cell type, and only in

the mammary gland. We don't see the expansion everywhere else in the body, even though NKT cells are present everywhere else in the body."

The team wanted to know what the larger number of NKT cells were doing in the breast tissue. Hanasoge discovered that in mice, breast epithelial cells, which line lactation ducts, produce a specific protein called CD1d after pregnancy. If the cells did not present CD1d, the researchers observed no increase in NKT cells in the tissue; the epithelial cells became cancerous and grew into tumors. Hanasoge and dos Santos think that CD1d molecules are calling in NKT cells to monitor the epithelial cells in the breast tissue after pregnancy. If they become cancerous, the NKT cells can quickly kill them to prevent tumor growth.

The team's findings establish a novel link between pregnancy and the immune system in preventing breast cancer. The dos Santos lab wants to know how these findings can be translated into humans and what other factors may influence an abundance of NKT cells in breast tissue, such as aging and menopause, which are both associated with increased breast cancer risk. Dos Santos says: "One of the hypotheses that we are working on now is: do pregnancies later on in life bring in the same expansion of the same subtypes of immune cells as pregnancies that took place early in life?"

The team published their findings on December 7, 2021, in *Cell Reports*.

Reference: "Parity-induced changes to mammary epithelial cells control NKT cell expansion and mammary oncogenesis" 7 December 2021, Cell Reports.
DOI: 10.1016/j.celrep.2021.110099

https://bit.ly/3yhXqLI

Edison was right: Waking up right after drifting off to sleep can boost creativity

The state between wakefulness and sleep is a sweet spot for problem-solving

When Thomas Edison hit a wall with his inventions, he would nap in an armchair while holding a steel ball. As he started to fall asleep and his muscles relaxed, the ball would strike the floor, waking him with insights into his problems. Or so the story goes.

Now, more than 100 years later, scientists have repeated the trick in a lab, revealing that the famous inventor was on to something. People following his recipe tripled their chances of solving a math problem. The trick was to wake up in the transition between sleep and wakefulness, just before deep sleep.

"It is a wonderful study," says Ken Paller, a cognitive neuroscientist at Northwestern University who was not part of the research. Prior work has shown that passing through deep sleep stages helps with creativity, he notes, but this is the first to explore in detail the sleep-onset period and its role in problem-solving.

In this transitional period, we are not quite awake, but also not deeply asleep. It can be as short as a minute and occurs right when we start to doze off. Our muscles relax, and we have dreamlike visions or thoughts called hypnagogia, generally related to recent experiences. This phase slips by unnoticed most of the time unless it is interrupted by waking. Like Edison, surrealist painter Salvador Dalí believed interrupting sleep's onset could boost creativity. (He used a heavy key instead of a metal ball.)

To see whether Dalí and Edison were right, researchers recruited more than 100 easy sleepers. The team gave them a math test that required them to convert strings of eight digits into new strings of seven by using specific rules in a stepwise manner, such as "repeat the number if the previous and next digit are identical." The volunteers weren't told that there was an easier way to get the right answers by following a hidden rule: The second number in their final string was always the same as the last number in the same string.

Those who didn't find the trick after 30 trials took a 20-minute

break resting in a chair in a dark room with their eyes closed. Each held a plastic bottle in their right hand while the researchers recorded their brain activity with electroencephalography helmets, which measure electrical waves produced by neural cells. They were also told to report aloud what was in their minds if they let the bottle fall (see video, below).

Most of those who napped reported various visions: dancing numbers and geometrical shapes, the Roman Colosseum, a hospital room with a horse. After the break, the participants went back to complete the math problems.

The researchers didn't see any connection between the content of people's visions and their performance on the task. But looking at brain activity, they found that those who napped and were interrupted during the first phase of sleep were three times better at finding the hidden key to the problem than those who remained awake. Twenty out of 24 of these nappers (83%) found the key, versus only 15 out of the 59 (30%) that stayed awake, the researchers report today in *Science Advances*.

The creative effect happened even for people who spent just 15 seconds in the first sleep stage. But the trick didn't work for those who reached later stages of sleep. "Our findings suggest there is a creative sweet spot during sleep onset," says author Delphine Oudiette, a sleep researcher at the Paris Brain Institute. "It is a small window which can disappear if you wake up too early or sleep too deep."

Contrary to the Edison tale, the eureka moment didn't come immediately after waking in this study. People took on average 94 trials of the math test after the nap to have an insight. "It is not like you can take a power nap and wake up with a solution right away," Oudiette says. (She has tried the technique herself a few times but thinks its application is tricky in real life, when the solutions to most of our problems aren't as well-defined as a math calculation.)

Still, sleep researcher Tore Nielsen at the University of Montreal was surprised that such short periods of sleep had such a significant effect. Scientists previously assumed it would take longer periods of sleep to help with problem-solving, says Nielsen, who was not involved with the work. He has adopted Edison's trick in his personal life, napping at his desk and waking up when his head falls forward to then write down his dreams. Now that the technique is validated, he says, it will make research on sleep and creativity easier.

The study team also identified a brain activity pattern linked to the creativity-boosting phase: moderate levels of brain waves at a slow frequency known as alpha, associated with relaxation, and low levels of delta waves, a hallmark of deep sleep.

Oudiette says researchers can now focus on this brain signature when investigating the neural mechanisms of creative problem-solving. Her team has already planned an experiment to help people reach a creative zone by monitoring their brain waves in real time. "Edison's intuition was somewhat right," she says, "and now we have a lot more to explore."

https://bit.ly/3oGMWC8

COVID-19 Breakthrough: Scientists Discover How the SARS-CoV-2 Virus Evades Our Immune System

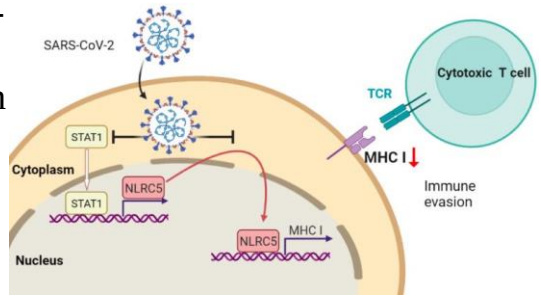
A discovery by researchers at the Texas A&M College of Medicine could lead to new therapies to prevent the virus from proliferating in the human body.

By Gracie Blackwell, Texas A&M College of Medicine

The immune system is a complex network of cells and proteins that is designed to fight off infection and disease, especially those like the coronavirus, or SARS-CoV-2, that can cause numerous issues in the human body. But many individuals are still at risk of being infected with the coronavirus, letting it replicate in the body and further transmitting to other individuals.

The underlying mechanism of how SARS-CoV-2 escapes from the immune system has been poorly understood. However, researchers from the Texas A&M University College of Medicine and Hokkaido University have recently discovered a major mechanism that explains how SARS-CoV-2 can escape from the immune system and replicate in the human body. Their findings were recently published in the journal *Nature Communications*.

"We found that the SARS-CoV-2 virus carries a suppressive gene that acts to inhibit a human gene in the immune system that is essential for destroying infected cells," said Dr. Koichi Kobayashi, adjunct professor at the College of Medicine and lead author of the paper.



SARS-CoV-2 escapes from immune responses by cytotoxic T cells via impaired MHC-I expression which is caused by reducing both the amount and function of NLRC5. **Credit: Koichi Kobayashi**

Naturally, the cells in a human's immune system are able to control virus infection by destroying infected cells so that the virus cannot be replicated. The gene that is essential in executing this process, called NLRC5, regulates major histocompatibility complex (MHC) class I genes, which are genes that create a pathway that is vital in providing antiviral immunity. Kobayashi and his colleagues discovered this in 2012.

"During infection, the amount and activity of NLRC5 gene become augmented in order to boost our ability of eradication of viruses," Kobayashi said. "We discovered that the reason why SARS-CoV-2 can replicate so easily is because the virus carries a suppressive gene, called ORF6, that acts to inhibit the function of NLRC5, thus inhibiting the MHC class I pathway as well."

Kobayashi, who holds a joint appointment as a professor at Hokkaido University in Japan, collaborated with Paul de Figueiredo, associate professor in the Department of Microbial Pathogenesis and Immunology at the College of Medicine, on this paper.

Kobayashi and his team's discovery shed light on the mechanism to how SARS-CoV-2 can replicate in the human body and can potentially lead to the development of new therapeutics to prevent the coronavirus from escaping the immune system and replicating in the body.

Although the introduction of COVID-19 vaccines, such as the Pfizer and Moderna vaccines, can lower an individual's chance of contracting the virus, there is currently no permanent therapy that can entirely prevent a human from contracting SARS-CoV-2.

"We hope that this new discovery will allow us to develop a new drug that can block this gene so our immune system will be able to fight off the coronavirus for good," de Figueiredo said.

Reference: "SARS-CoV-2 inhibits induction of the MHC class I pathway by targeting the STAT1-IRF1-NLRC5 axis" by Ji-Seung Yoo, Michihito Sasaki, Steven X. Cho, Yusuke Kasuga, Baohui Zhu, Ryota Ouda, Yasuko Orba, Paul de Figueiredo, Hirofumi Sawa and Koichi S. Kobayashi, 15 November 2021, Nature Communications. DOI: 10.1038/s41467-021-26910-8

https://bit.ly/3dXjAtn

Primates vs Cobras: How Our Last Common Ancestor Built Venom Resistance After Long Evolutionary Arms Race

The last common ancestor of chimps, gorillas, and humans developed an increased resistance toward cobra venom, according to University of Queensland-led research.

Scientists used animal-free testing techniques to show that African and Asian primates evolved resistance toward the venoms of large, daytime-active cobras and discovered that our last common ancestor with chimps and gorillas evolved even stronger resistance.

University of Queensland PhD candidate Richard Harris said

African and Asian primates developed venom resistance after a long evolutionary arms race.

"As primates from Africa gained the ability to walk upright and dispersed throughout Asia, they developed weapons to defend themselves against venomous snakes, this likely sparked an evolutionary arms race and evolving this venom resistance," Mr. Harris said.

"This was just one of many evolutionary defenses – many primate groups appear to also have developed excellent eyesight, which is thought to have aided them in detecting and defending themselves against venomous snakes.

"But Madagascan Lemurs and Central and South American monkeys, which live in regions that haven't been colonized by or come in close contact with neurotoxic venomous snakes, didn't evolve this kind of resistance to snake venoms and have poorer eyesight.

"It's been long-theorized that snakes have strongly influenced primate evolution, but we now have additional biological evidence to support this theory."

The team studied various snake toxin interactions with synthetic nerve receptors, comparing those of primates from Africa and Asia with those from Madagascar – which doesn't have venomous snakes – and those from the Americas – where the cobra-related coral snakes are small, nocturnal, and burrowing.

Team leader Associate Professor Bryan Fry said the study also revealed that in the last common ancestor of chimpanzees, gorillas, and humans, this resistance was sharply increased.

"Our movement down from the trees and more commonly on land meant more interactions with venomous snakes, thus driving the evolutionary selection of this increased resistance," Dr. Fry said.

"It is important to note that this resistance is not absolute – we are not immune to cobra venom, just much less likely to die than other primates.

"We have shown in other studies that resistance to snake venoms comes with what's known as a fitness disadvantage, whereby the receptors don't do their normal function as efficiently, so there is a fine balance to be struck where the gain has to outweigh the loss.

"In this case, partial resistance was enough to gain the evolutionary advantage, but without the fitness disadvantage being too taxing.

"We are increasingly recognizing the importance snakes have played in the evolution of primates, including the way our brain is structured, aspects of language, and even tool use.

"This work reveals yet another piece in the puzzle of this complex arms race between snakes and primates."

Reference: "Monkeying around with venom: an increased resistance to a-neurotoxins supports an evolutionary arms race between Afro-Asian primates and sympatric cobras" by Richard J. Harris, K. Anne-Isola Nekaris and Bryan G. Fry, 25 November 2021, BMC Biology. DOI: 10.1186/s12915-021-01195-x

The research was a collaboration between UQ and Oxford-Brookes University's Dr. Anna Nekaris.

https://bit.ly/3pNj8TN

Can Prozac treat COVID? Perhaps, but a related drug may be better

It's early days yet. But here's what we know so far.

Jennifer Martin* **Richard John Head****

The rise of Omicron, the latest SARS-CoV-2 variant of concern, reminds us how quickly things can change during the pandemic.

Only a few weeks ago, we were hearing about a range of potential new COVID-19 antiviral drugs and antibody treatments. Now researchers are asking if such drugs will still work to treat Omicron, with its multiple new mutations. We'll be hearing more about this in coming weeks.

However, another approach to treating COVID is to "treat the host". Rather than target the virus itself, this involves treating the body's overwhelming response to the virus. This approach is less

susceptible to new viral variants.

And for this, we have some progress with, at first glance, an unlikely group of drugs to treat COVID-19 – antidepressants. These include fluoxetine (for example, Prozac) and the related drug fluvoxamine (for example, Luvox). It's early days yet. But here's what we know so far.

How could antidepressants treat COVID?

The antidepressants under investigation are SSRIs or selective serotonin reuptake inhibitors. These commonly prescribed mood-altering drugs block "reuptake" of the naturally occurring chemical messenger, serotonin, by nerve cells in the brain; some antidepressants stop serotonin being broken down. These mechanisms leave more serotonin available to pass messages between nearby nerve cells.

There are two ways SSRIs could have an effect on COVID-19.

First, human biology is frugal

Biological "frugality" sets the scene. It takes a lot of effort for the body to make a single important molecule and a huge undertaking if you need hundreds of them. So, biology directs important molecules to multi-task.

For example, we all make serotonin by introducing a few changes to the chemical structure of the essential amino acid tryptophan, commonly present in food.

Serotonin is then tasked with being:

- ***a messenger in the brain***
- ***a molecule to cause contraction in the gut***
- ***an inducer of platelet clotting, and***
- ***a modulator of how blood vessels work, including how they constrict and how they interact with the immune system.***

The virus responsible for COVID-19 drives a devastating hyperinflammation in serious disease. This involves many of the systems serotonin strongly regulates – inflammation, platelet clotting and proper functioning of blood vessels.

So there's a potential link between drugs that influence serotonin, and COVID-19.

Second, drugs can open different locks

Drugs often act as a "key" to open certain locks in the body. However, in some cases, the "key" is not that specific and can surprise us by opening additional, unrelated locks.

This is called a pleiotropic response and is the basis of using existing drugs for new purposes (repurposing).

This may also explain why a mood-altering drug may be effective in serious infection. As we'll see later, it may open the lock to influence inflammation.

Sometimes drugs act as 'keys' that open different, unrelated locks.

Have people tried SSRIs for COVID?

There have been a number of clinical trials showing favourable COVID-19 outcomes for people taking SSRIs.

In a preliminary study, outpatients with COVID-19 symptoms treated with fluvoxamine were less likely to deteriorate over 15 days compared with those taking the placebo.

Another study found patients hospitalised for COVID-19 who took antidepressants – including the SSRI fluoxetine, and non-SSRI antidepressants – within 48 hours of admission were less likely to be intubated or die than those who didn't take an antidepressant.

The latest evidence comes from a major independent study published online in late October. This found people diagnosed with COVID-19 who took fluvoxamine reduced their chance of symptoms deteriorating or needing to go to hospital, compared to those who took the placebo.

Although few studies have directly compared fluvoxamine with fluoxetine to treat COVID-19, the bulk of the best quality evidence suggests to date suggests fluvoxamine may have the greatest promise.

However, there are a number of studies on broader effects of other SSRIs including fluoxetine.

What could be happening?

It is likely our frugal biology is at work, in particular the influence of serotonin on platelets and blood clotting.

SSRIs may be reducing the incidence or size of blood clots, heart attacks and strokes we'd usually see in severe COVID-19.

SSRIs could also switch on anti-inflammatory pathways in the body, independent of any serotonin effect. Different SSRIs have different capacities to do this, which may explain why some SSRIs seem to have a greater effect on COVID-19 than others.

For instance, fluvoxamine is a more powerful key to unlock the sigma-1 receptor, which has a significant role in controlling inflammation. Fluvoxamine may also increase melatonin, which has anti-inflammatory effects.

What we still want to find out

Despite promising clinical trials, in particular for fluvoxamine, researchers still want to know:

- ***is this a class effect? In other words, would all SSRIs work? Although fluvoxamine is widely available, it is not on the World Health Organization's list of essential medicines, whereas fluoxetine is. So we need to know if these drugs are interchangeable within the class of SSRIs, or even with antidepressants more broadly***
- ***we still don't know the precise mechanism behind why these drugs seem to work. But how much more data would we need before we start treating these patients in hospital?***
- ***could fluvoxamine work for vaccinated people? Or is the potential mainly for those unvaccinated, and more likely to have severe disease?***
- ***we need further information on possible side-effects of using SSRIs in COVID-19 patients, particularly if we are using doses different to the standard antidepressant dose. However, since SSRIs are existing and commonly used drugs, we already know a lot about how they work in the body, and any possible adverse reactions.***

That said, based on the results to date with fluvoxamine in particular, we consider it needs to be added to the list of candidate COVID-19 drugs for further testing and evaluation.

Omicron may not be the last variant of concern. And by "treating the host" with existing drugs – SSRIs being just one example – we can offer patients options that are not at the mercy of future, unknown variants.

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A New Type of Omicron Has Now Emerged in Multiple Countries

A new version of the Omicron coronavirus variant was designated on Tuesday that experts say will be harder to track because of its genetics.

Marianne Guenot, Business Insider

The new lineage, called BA.2, has been spotted seven times so far across South Africa, Australia, and Canada.

BA.2 is genetically quite different from the original Omicron lineage, now called BA.1, which has been spreading across the world, said Francois Balloux, the director of the University College London Genetics Institute, per *The Guardian*.

Crucially, it doesn't have the characteristic S-gene dropout mutation which allows Omicron BA.1 to be easily identified via PCR test results, the main way the variant has been tracked so far. That means that "the two lineages may behave differently," he said, *The Guardian* reported.

While the change will make tracking harder, it is "nothing to be scared of yet" said Vinod Scaria, a clinician and computational biologist at the CSIR Institute of Genomics and Integrative Biology, in a tweet.

David Stuart, a professor of structural biology at Oxford University, agreed. "I don't think there's any reason to think that the new outlier is any more of a threat than the form of Omicron that's knocking around at the moment in the UK," he said, per the *Financial Times*. "But it is terribly early," he added.

PCR tests should still pick up this variant but might not be able to distinguish it from others

BA.2 carries "many of the defining mutations" of Omicron, according to Andrew Rambaut, an evolutionary biologist at the University of Edinburgh, UK, who reviewed the mutations in a blog post. But it also has dozens of mutations BA.1 doesn't have and dropped dozens that do appear on BA.1. Most notably, BA.2 is lacking the specific mutation that scientists were using as a quick way to track Omicron: the 69/70del mutation on the S gene, as Insider previously reported.

PCR tests check for different markers to see if someone is carrying the coronavirus, one of which targets the S gene. When someone with the BA.1 lineage of Omicron gets a PCR test, one of the markers won't work: this is called an S-gene dropout.

This was an easy way to separate Omicron from other variants currently circulating, most of which wouldn't cause this S-gene dropout. But this likely won't be the case for the BA.2 lineage. That means scientists will have to depend on more time-consuming and less widespread sequencing to identify it.

For Emma Hodcroft, an evolutionary geneticist at the University of Basel, that means that "there may be more Omicron than we think," per the *Financial Times*.

She told that outlet that "from the numbers we have right now, I don't think there's a very large hidden burden from BA.2."

In a tweet, Hodcroft emphasized that PCR tests should still work to detect whether someone has the coronavirus, even with this new lineage. "This means we can't use this 'shortcut' to find possible Omicron cases for BA.2 only. However, the PCR test itself still works!" she said.

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https://wb.md/3lVyOU6

Daytime Eating May Cut Diabetes Risk in Night-Shift Workers

Daytime eating may help night-shift workers avoid having a misaligned internal circadian clock and impaired glucose tolerance

Marlene Busko

By only eating during the daytime, night-shift workers might avoid having a misaligned internal circadian clock and impaired glucose tolerance — which are typical in night-shift workers — a small clinical trial suggests.

Among 19 healthy young adults who spent 2 weeks in a controlled laboratory setting that included a simulated night shift, the nine individuals who ate their three meals and a snack during the day (7 AM to 7 PM) did not have a misaligned circadian rhythm or glucose intolerance, unlike the 10 individuals who ate the same food during the day and night.

The study was published December 3 in *Science Advances*.

The findings suggest that nighttime eating caused a misalignment between the body's central circadian "clock" (located in the hypothalamus) and sleep/wake, light/dark, and fasting/eating cycles

that can influence peripheral "clocks" throughout the body.

"These results indicate that meal timing was primarily responsible for the reported effects on glucose tolerance and beta-cell function, possibly due to the misalignment of central and peripheral 'clocks' throughout the body," said senior author Frank A.J.L. Scheer, PhD.

"While the central circadian 'clock' was still on Boston time, the endogenous circadian glucose rhythms suggest that some peripheral 'clocks' — as perhaps those in the liver — had dramatically shifted to a time zone in Asia," explained Scheer, director of the Medical Chronobiology Program in the Division of Sleep and Circadian Disorders at Brigham and Women's Hospital, Boston, Massachusetts in a press release issued by the hospital.

Meal Timing Could Counteract Negative Effects of Night Shift

"This is the first study in humans to demonstrate the use of meal timing as a countermeasure against the combined negative effects of impaired glucose tolerance and disrupted alignment of circadian rhythms resulting from simulated night work," he added in a press release from the National Heart, Lung, and Blood Institute, the main study funder.

"Night-shift workers often reschedule their meal intake to the nighttime, as they are awake during those hours," lead author of the work, Sarah L. Chellappa, MD, PhD, added.

"This study reinforces the notion that when you eat matters for determining health outcomes such as blood sugar levels, which are relevant for night workers as they typically eat at night while on shift," said Chellappa, a researcher who previously worked with Scheer and is currently working in the nuclear medicine department at the University of Cologne, Germany.

"Our findings," the researchers summarize, "may help in the development of evidence-based circadian strategies (eg, timing of eating) to prevent glucose intolerance in individuals experiencing circadian rhythm disruption."

"Future translational studies with individuals undergoing real-life shift work schedules (eg, permanent, rotating or irregular night shifts, morning shifts, and evening shifts) are required to establish if our reported beneficial effects on glucose tolerance (as well as other health and performance outcomes) apply to this vulnerable population," they conclude.

Could Meal Timing Mitigate Effects of Shift Work?

Previous studies have shown that in night-shift workers the central circadian clock is misaligned with daily behaviors, and these individuals have impaired glucose tolerance and an increased risk of diabetes. But it was not clear if avoiding nighttime eating might lessen this risk.

To investigate, researchers recruited 19 healthy young participants (12 men, seven women) for the clinical trial during 2015 to 2018.

Participants were a mean age of 26.5 years, had a mean body mass index of 22.7 kg/m^2, and had an A1c between 4.9% and 5.4%.

They underwent a stringently controlled circadian laboratory protocol, where they remained in individual suites in an environment free of time cues. When they were not involved in study tasks, they could read, write, watch movies, or do crafts.

First, participants stayed awake for 32 hours in a highly controlled, dimly lit environment, where they kept constant body posture and consumed identical snacks every hour, as part of a "constant routine" protocol.

After that, they underwent simulated night-shift work. Participants in one group ate scheduled meals during the day and night. The other participants ate meals during the day only, aligned with the approximately 24-hour cycle of the central circadian "clock."

Participants then followed a second "constant routine" protocol to assess the aftereffects of the two different meal schedules on endogenous circadian rhythms.

During the simulated night shift, the average glucose levels of the

participants who ate during the day and night increased by 6.4% from baseline, whereas these levels did not increase significantly in the participants who only ate during the day.

This study was funded by the National Institutes of Health, the Alexander von Humboldt Foundation, the American Diabetes Association, the Spanish Government of Investigation, Development and Innovation, the Autonomous Community of the Region of Murcia through the Seneca Foundation, and the Oregon Institute of Occupational Health Sciences. Scheer has reported receiving lecture fees from Bayer HealthCare, Sentara HealthCare, Philips, Vanda Pharmaceuticals, and Pfizer. Disclosures for the other authors are listed with the article. Sci Adv. Published online December 3, 2021. Article

https://wb.md/3DKQ5VZ

Coronavirus Attacks Fat Tissue, Study Says

The coronavirus infects fat cells and certain immune cells within body fat, creating an immune response that could lead to major damage, according to a recent preprint study.

Carolyn Crist

The finding could explain why those who are overweight or obese face higher risks for severe illness and death from COVID-19. The study hasn't yet been peer-reviewed or published in a journal, but it offers insight into why some patients are vulnerable, even if they don't have any other risks or conditions.

"The bottom line is, 'Oh my God, indeed, the virus can infect fat cells directly,'" Philipp Scherer, PhD, a scientist who studies fat cells at UT Southwestern Medical Center in Dallas, told *The New York Times.*

"Whatever happens in fat doesn't stay in fat," he said. "It affects the neighboring tissues as well."

In the study, researchers from the Stanford University School of Medicine tested fat tissue from bariatric surgery patients to understand whether they could become infected with the coronavirus. They looked at different types of cells — adipocytes, or fat cells, as well as pre-adipocytes that become fat cells and immune cells called adipose tissue macrophages.

The research team found that the adipocytes could become infected, though they didn't become overly inflamed. But certain immune cell macrophages could be infected and have a major inflammatory response. Beyond that, the pre-adipocytes weren't infected, but they added to the inflammatory response.

The researchers also looked at fat tissue from the bodies of European patients who died from COVID-19 and found the coronavirus in fat around various organs, including the heart and intestines. That could be linked with the organ damage seen in severe COVID-19 patients, they wrote.

The coronavirus appears to evade the body's immune defenses and "hang out" in fat tissue, which allows it to replicate and trigger a severe immune response, David Kass, MD, a professor of cardiology at Johns Hopkins Medicine, told the *Times*.

"If you really are very obese, fat is the biggest single organ in your body," he said.

The coronavirus "can infect that tissue and actually reside there," he continued. "Whether it hurts it, kills it, or at best, it's a place to amplify it — it doesn't matter. It becomes kind of a reservoir."

The infected body fat could contribute to "long COVID," which has led to symptoms that last for weeks or months after someone has recovered from a coronavirus infection, the study authors wrote.

The findings could open avenues for new COVID-19 treatments that target body fat, they said. Drugs that ease inflammation of the adipose tissue in obese patients could help COVID-19 patients, they wrote.

What's more, the study may show that health care professionals should consider a patient's weight and body fat when giving COVID-19 vaccines and treatments, the *Times* reported.

"This paper is another wake-up call for the medical profession and public health to look more deeply into the issues of overweight and obese individuals, and the treatments and vaccines we're giving them," Barry Popkin, PhD, an obesity researcher at the University

of North Carolina at Chapel Hill who has studied COVID-19 risks for overweight and obese patients, told the newspaper.

"We keep documenting the risk that they have, but we still aren't addressing it," he said.

Sources:

BioRxiv: "SARS-CoV-2 infects human adipose tissue and elicits an inflammatory response consistent with severe COVID-19."

The New York Times: "The Coronavirus Attacks Fat Tissue, Scientists Find."

https://wb.md/3ERccLJ

Pollutants Tied to Changes in Ratio of Boys to Girls Born

Certain chemical pollutants were related to fewer boys being born compared with girls when researchers looked at data

Damian McNamara, MA

The season of conception does not affect whether more boys than girls are born, nor do temperatures in the environment, a large study reveals. Similarly, researchers found no connection with a location's violent crime level, unemployment rate, or major events like Hurricane Katrina.

But certain chemical pollutants were related to fewer boys being born compared with girls when researchers looked at data for more than 3 million newborns over 8 years in the US and another 3 million born over 30 years in Sweden.

"With data on births in 150 million people in the US over 8 years and 9 million Swedes over 9 years, this is almost surely the largest study to date on the question of environmental factors and their influence on sex ratio at birth," said Shanna Swan, PhD, who was not affiliated with the research

Variations in the annual sex birth ratio (SRB) — the number of boys born compared with the total birth rate — are well-accepted. Less clear is what things drive these changes.

Although not the first study to look for connections between major events or pollutants in the air, water, and land and the SRB, it is the first to mine two very large electronic medical record databases for answers, senior study author Andrey Rzhetsky, PhD, a professor of medicine and human genetics at the University of Chicago, told *Medscape Medical News.* The findings were published December 2 in *PLOS Computational Biology*.

And even though the SRB did not vary significantly after Hurricane Katrina in 2005, it did after the 2007 shooting at Virginia Tech, Rzhetsky and colleagues found. The SRB was lower than expected 34 weeks after the mass shooting.

Location, Location, Location

The researchers also found that the levels of chemical pollutants "varied remarkably" across different regions of the country. For example, lead in the land was elevated in the Northeast, Southwest, and Mideastern US, but not in the South. Also, the highest levels of total mercury in water samples was found mostly in Eastern states, especially in the Northeast.

Rzhetsky and colleagues mapped the regional differences of many factors, including hydrazine. Hydrazine is a foaming agent used to make pharmaceuticals and agrochemicals and is used as a propellant for spacecraft. "Hydrazine appears to follow capricious, blotch-like shapes in the eastern US, each blotch likely centered at a factory emitting this pollutant," the authors write.

To get a more complete picture, the investigators also compared changes in the SRB with data from the US National Oceanic and Atmospheric Administration, US Environmental Protection Agency, Swedish Meteorological and Hydrological Institute, and Statistics Sweden.

They found that aluminium in air, chromium in water, and total mercury levels drove the SRB up. By comparison, lead in soil and areas with a higher renter occupancy were linked to a lower SRB, or a higher proportion of girls being born.

Rzhetsky and colleagues also add to the evidence for a link between

polychlorinated biphenyls (PCBs) and the SRB. Previous findings conflict, the authors note. "Since the sample sizes of the studies published thus far were very small, our PCBs result would have substantially larger statistical power," they write.

Several pollutants had no significant link to SRB in the study, including levels of lead or chromium in the air, arsenic in the soil, and cadmium in the air or water.

Consistent Findings

That said, the research had limits.

"The magnitude is new in terms of number of births, and the statistical methods are unusually sophisticated, but the conclusions don't really differ from much of what has been published," said Swan, a professor of environmental medicine and public health at the Icahn School of Medicine at Mount Sinai in New York City.

"The takeaway message that many examined exposures are associated with lower — and some with higher — SRBs is not new, but consistent with other, smaller studies," said Swan, who co-authored a September 2021 study evaluating endocrine-disrupting chemicals and lower birth rates in Asia.

The data on environmental exposures "is, however, quite uneven, and only known at the ecologic and not the individual level," she said. "We learn, for example, that SRB was significantly reduced...among families living in areas with the highest septile of lead exposure, but also in those among the highest septile of percent renter occupancy." "Evaluating these as to mechanism and plausibility is difficult," Swan said.

More Research Warranted

The mechanism remains unknown, but the investigators suggested that female embryo pregnancies may end early in development, driving the SRB up. Also, male embryo deaths are more common in the late second or third trimester, at which point they would drive the SRB down. A third factor, maternal hormone levels around the time of conception, could also alter the SRB.

The associations between individual factors and SRB changes are just that — associations — not intended to be interpreted as "sex-specific selection mechanisms" causing the differences at this point, the authors noted. Further studies to confirm the associations are needed.

The research is a good stepping-off point for future studies to look closer at the contribution of pollutants like arsenic, lead, cadmium, and more, Rzhetsky said.

Damian McNamara is a staff journalist based in Miami. He covers a wide range of medical specialties, including infectious diseases, gastroenterology, and critical care. Follow Damian on Twitter: @MedReporter.

PLoS Comput Biol. 2021;17(12):e1009586. Full text

https://bit.ly/3yqWPcV

Scientists Say We Should Rethink Moons as Planets... And Reinstate Pluto

The International Astronomical Union (IAU) has a very strict definition of the word "planet".

Michelle Starr

According to the definition – drafted, tweaked, and agreed upon in August 2006 – an astronomical body is officially a planet if it orbits the Sun, has sufficient mass to be spherical, and has cleared the neighborhood around its orbit.

Under these strictures, only eight bodies in the Solar System can be considered planets: Mercury, Venus, Earth, Mars, Jupiter, Saturn, Uranus and Neptune.

This definition very effectively cut out Pluto, a move that has proven, at the very least, extremely controversial, with many scientists calling for a more inclusive redefinition based solely on the physical properties of the body in question.

Which brings us to a new paper that has bolstered those bids with an in-depth analysis of the IAU criteria. Those criteria, the paper finds, are not based on science after all; instead, they rely on

folklore and astrology.

Led by planetary scientist Phillip Metzger of the University of Central Florida, the researchers urge that the third criterion in particular be rescinded, and the definition of a planet be simplified: that the body is, or has been, geologically active.

This would put many Solar System bodies in the planet category, including Earth's Moon and many other moons, dwarf planets, and even asteroids – an outcome that has previously been used as an argument against expanding the definition.

But the fact that these bodies are similar enough that they could be grouped together is a compelling reason why they should be, the researchers behind the new study say.

"It's like defining 'mammals,'" Metzger says. "They are mammals whether they live on the land or in the sea. It's not about their location. It's about the intrinsic characteristics that make them what they are."

Over a period of five years, the team conducted an in-depth review of the last 400 years of scientific literature on planets. They found that, gradually over time, the definition set by Galileo in the 1630s has been chipped away.

Planets, Galileo argued, are objects made of elements that change over time, much as Earth does. Or, as the researchers interpret it, they are geologically active. They also cite Galileo's argument that planets reflect sunlight, rather than producing light of their own.

This definition was in use until the 20th century, the researchers point out. When Pluto was discovered in 1930, it was categorized as a planet. But between 1910 and the 1950s, the researchers found that there was a declining interest in planetary science, at least as far as the literature goes – the number of papers published in this time dwindled.

"We've shown through bibliometrics that there was a period of neglect when astronomers were not paying as much attention to planets," Metzger says. "And it was during that period of neglect that the transmission of the pragmatic taxonomy that had come down from Galileo got interrupted."

That vacuum, the paper asserts, was filled by folklore. In the previous two centuries, almanacs had become popular – annual books that made meteorological and other predictions based on the positions of a small number of planets. Astrology, in other words.

This introduced and cultivated the perception that only the largest bodies orbiting the Sun were planets. Anything else, such as moons and asteroids, were not.

And this, they suggest, crept into the scientific literature.

"This might seem like a small change, but it undermined the central idea about planets that had been passed down from Galileo," Metzger says.

"Planets were no longer defined by virtue of being complex, with active geology and the potential for life and civilization. Instead, they were defined by virtue of being simple, following certain idealized paths around the Sun."

The geophysical definition started to rise again in the 1960s, when scientific interest in Solar System exploration was renewed, causing a split in scientific thought. The IAU definition in 2006 sought an end to the argument, but that obviously hasn't happened.

One could argue that our understanding of the different kinds of rocks in the Solar System is a lot more sophisticated than it was in Galileo's day. But the criterion of "clearing the orbital neighborhood" is not where that argument should lead, the researchers say. Instead, this criterion was developed to keep the number of planets small and manageable, and that's bad science.

"When Galileo proposed that planets revolve around the Sun, and reconceptualized Earth as a planet, it got him jailed under house arrest for the rest of his life," Metzger says.

"When scientists adopted his position, he was vindicated, in a sense,

let out of jail. But then around the early 1900s, we put him back in jail again when we went with this folk concept of an orderly number of planets. So, in a sense, we rejailed Galileo.

"So, what we're trying to do, in a sense, is get Galileo out of jail again, so that his deep insight will be crystal clear."

The authors, all experts in fields of space research, might have their interpretation of science history challenged by others in the research community, however, who are likely to have their own alternative takes on how voices, fashions, and beliefs in the past inform the way we now categorize nature.

But as the study authors put it, definitions matter. They shape how we observe, theorize, and think about nature on a fundamental level. It's a paper that will no doubt ruffle a few feathers, and keep the debate over planets going for a while to come yet.

The paper has been published in *Icarus*, and supplementary data published online in full on Metzger's website.

https://bit.ly/3IGYxJA

Meat-eating dinosaurs were terrifyingly fast, footprints reveal

Theropod tracks provide a snapshot of dinosaurs' running speeds.

By Mindy Weisberger

Three-toed, meat-eating dinosaurs may have sprinted as fast as a car driving on city streets, new research shows. That finding comes from analyzing the footprints these theropods left behind as they dashed over squishy lake bed mud tens of millions of years ago.

Reconstruction of an indeterminate theropod running on lake bed sediments during low water timespan. **(Image credit: Pablo Navarro-Lorbés)**

Two sets of fossilized footprints at a site in La Rioja, Spain show that the makers of the tracks were galloping along at speeds up to 27.7 mph (44.6 km/h), reaching "some of the top speeds ever calculated for theropod tracks," according to the new study.

According to researchers' analysis of the tracks, one dinosaur sped up steadily and consistently as it ran, while the other quickly changed its speed while still on the move. Together, these two sets of footprints from the early part of the Cretaceous period (145 million to 66 million years ago) offer a unique snapshot of dinosaur mobility and behavior.

Paleontologists use several methods to calculate running speeds in extinct dinosaurs, said Pablo Navarro-Lorbés, a researcher at the University of La Rioja in Logroño, Spain and lead author of the new study. One method builds biomechanical models based on dinosaur bones and limb proportions, "and the other main one is the speed estimation from tracks," Navarro-Lorbés told Live Science in an email.

One set of the La Rioja tracks, dubbed La Torre 6A-14, preserves five three-toed footprints that were each about 12.9 inches (32.8 centimeters) long and 11.9 inches (30.2 cm) wide. The other trackway, La Torre 6B-1, includes seven three-toed footprints that were a little smaller, measuring 11.4 inches (28.9 cm) long and 10.6 inches (26.9 cm) wide. Based on the size of the prints, hip height of the theropods would have been between 4 to 5 feet (1.1 to 1.4 meters), so the animals would have stood about 7 feet (2 m) tall and measured around 13 to 16 feet long (4 to 5 m) "from the snout to the tip of the tail," Navarro-Lorbés said.

While it isn't possible to tell what genus of theropod made the tracks, similarities between the footprints hinted that the two dinosaurs belonged to the same taxonomic group, were non-avian — not one of the lineages directly related to modern birds — and were "very agile," according to the study.

To calculate the theropods' running speeds, the researchers used a formula that incorporated the dinosaurs' hip heights and stride

length. This enabled them to not only calculate the animals' speed with every step but also detect speed variations "like acceleration or deceleration," Navarro-Lorbés explained. They found that the dinosaur that made the 6A-14 trackway reached just over 23 mph (37 km/h), while the speedier 6B-1 dinosaur scampered into the lead with a top speed of nearly 28 mph (45 km/h). By comparison, the fastest speed ever clocked in a human runner is 27.5 mph (44.3 km/h), which was achieved very briefly by the famed Jamaican sprinter Usain Bolt in 2009, according to The New York Times.

***One of the footprints of the 6A tracksite. Scale bar is 10 centimeters.* (Image credit: Pablo Navarro-Lorbés)**

But while Bolt's running prowess has been well-documented, extinct dinosaurs aren't so lucky. Trackways that can reveal their running speeds are exceptionally rare, so these footprints from northern Spain provided a unique opportunity for the researchers to corroborate theropod speed estimates that were previously produced by other scientists who were analyzing the animals' bones, Navarro-Lorbés said.

"Fast-running theropod tracks are scarce in the fossil record," Navarro-Lorbés said. "Being able to study them and confirm some other studies made from different approaches are great news for us." The findings were published online Thursday (Dec. 9) in the journal Nature.

https://bit.ly/3oM5FfA

Legendary Flying Reptile: Fleshing Out the Bones of Quetzalcoatlus, Earth's Largest Flier Ever

70 million-year-old fossils reveal unique walking behavior of this huge, heron-like pterosaur.

Look around any wetland today and you're likely to see 3-foot-tall egrets or 4-foot-tall herons wading in the shallows in stealthy search of fish, insects or crustaceans.

But 70 million years ago, along the Rio Grande River in Texas, a more impressive and scarier creature stalked the marshes: the 12-foot-tall pterosaur known as *Quetzalcoatlus*. With a 37- to 40-foot wingspan, it was the largest flying animal that ever lived on Earth.

***An artist's rendition of Quetzalcoatlus northropi, a type of pterosaur and the largest flying animal that ever lived on Earth. Quetzalcoatlus stood about 12 feet tall and walked with a unique gait because of its enormous 20-foot wings, which touched the ground when folded.* Credit: Artwork courtesy of James Kuether**

In six papers published this week as a *Memoir* by the Society of Vertebrate Paleontology, scientists and an artist provide the most complete picture yet of this dinosaur relative, the largest example of which is represented by just a single set of fossilized bones collected in the late 1970s from Big Bend National Park. The papers describe the pterosaur's geological and ecological setting during the Upper Cretaceous, its anatomy and taxonomic position, and how it moved on the ground and in the air.

One of the papers, co-authored by University of California, Berkeley, paleontologist Kevin Padian, emeritus professor of integrative biology and emeritus curator in the UC Museum of Paleontology, answers some of the mysteries surrounding the flying and walking behavior of this unique animal, about which little has been published since its discovery more than 45 years ago. How can an animal walk with wings so long that they touch the ground when folded? What did it eat, and how did it feed? How strong a flier was it? And how does an animal whose wings span 40 feet, yet whose legs are only 6 feet high at the hip, launch itself into the air?

"This ancient flying reptile is legendary, although most of the public conception of the animal is artistic, not scientific," said Padian, who co-edited the monograph. "This is the first real look at the entirety of the largest animal ever to fly, as far as we know. The results are revolutionary for the study of pterosaurs — the first animals, after insects, ever to evolve powered flight."

The original *Quetzalcoatlus* fossils were discovered by Douglas Lawson, who at the time was a 22-year-old studying for a master's degree in geology at the University of Texas, Austin, and later became a doctoral student at UC Berkeley. The fossil pterosaur — which he named after the Aztec flying serpent god — consisted of a partial wing that implied a size comparable to that of some airplanes and was at least 50% bigger than the wings of the largest known bird, an extinct and much larger relative of living condors and a descendent of the dinosaurs.

Unlike the serpent god, *Quetzalcoatlus* had no feathers: Its body, including wings of skin and fibers of keratin, was covered with hair, as in all pterosaurs. Like dinosaurs, it was likely warm- blooded and active. It had lost its tail, presumably to improve its maneuverability, and its 6-foot neck and 4-foot crested skull suggest a stork on steroids.

Wann Langston, for many years a curator of UT Austin's Vertebrate Paleontology Laboratory, invited many colleagues, including Padian, to work on the fossils, but was unable to publish a full description of the animal before his death in 2013.

At the request of the laboratory, Padian teamed up with engineer and amateur paleontologist James Cunningham and London artist John Conway — all longtime colleagues of Langston — to look at the fossilized bones of Lawson's find, *Quetzalcoatlus northropi,* and compare them with more numerous specimens of a smaller *Quetzalcoatlus* species in order to better understand feeding, flying, walking and launch behavior. Langston is listed as a fourth co-author of the paper.

"Jim and John and I came to the project with very different ideas," Padian said, "but we didn't put a single statement in our paper unless all three of us agreed on it."

Playing with the bones

To understand how the *Quetzalcoatlus* pterosaurs behaved, Padian and colleagues manipulated casts of bones from about a dozen smaller and more complete pterosaur fossil skeletons, including those of the species *Quetzalcoatlus lawsoni*, which is newly-named after Lawson in one of the accompanying papers. The *Q. lawsoni* fossils were found in the same Javelina Formation in West Texas around the time the larger *Q. northropi* was excavated. The smaller specimens are half the size of the larger one Lawson initially found, but they consist of about 300 fossilized bone bits. The larger animal, however, is known only from a few wing bones: a humerus and an ulna from the upper arm and forearm, respectively.

The picture that Padian, Cunningham and Conway paint is of an animal similar to egrets and herons in how it feeds and launches itself into the air, like condors and vultures in how it soars, but, because of its enormous wings, unlike any other known animal in how it walks.

"Pterosaurs have huge breastbones, which is where the flight muscles attach, so there is no doubt that they were terrific fliers," he said. "Their upper arm bone — the humerus — has huge, bony crests for anchoring the flight muscles, which are larger than those of birds and far larger than those of bats. The wings worked essentially like those of birds and other dinosaurs, to which pterosaurs are most closely related. Despite two centuries of reconstructing pterosaurs like bats, there is no evidence for this view: Bats are unique and very different from birds and pterosaurs."

Like birds and bats and even humans, the forelimbs of pterosaurs have three segments: the upper arm or humerus, from the shoulder

socket to the elbow; the forearm, including the radius and ulna; and the wrist and hand bones. But unlike birds and bats, the leading edge of the outer part of the pterosaur wing is formed by a giant wing-finger. “It’s like having a ski pole extended from the base of your fingers and angled 90 degrees outward,” Padian said.

Quetzalcoatlus was bipedal, that is, it walked on two legs. But because its forelimb bones are so elongated, its wings could not avoid touching the ground when folded. This four-point stance suggested to some that the pterosaurs walked like a vampire bat, which uses its forelimbs to propel itself forward on the ground. But study of the bones shows that the pterosaur could not have used the wings for propulsion. When grounded, they could only move their wings forward or to the side.

“Once you put the forelimbs on the ground in these pterodactyls, you can’t rotate the forelimb back to push the animal forward like any sensible quadruped because there’s a bone in the way in the shoulder,” Padian said. That doesn’t mean they were clumsy.

“To avoid tripping, the animal first raised its left arm, then advanced its left leg in a full step, then it placed the hand on the ground,” he said. “The process was repeated with the right limb: The right arm lifted, the right leg advanced and emplaced the right foot, and then the right hand descended. It seems a cumbersome process to us, but the animal could execute the gait quickly and easily.” This fits perfectly with trackways of walking pterosaurs discovered in Southern France in the 1990s, Padian said.

Powerful legs provide a jump-start

However, because its legs were shorter than its wings, taking off was not as simple as flapping to generate lift.

“There are problems with a running takeoff. In the smaller specimens, you’re looking at a 9-foot wing that’s probably flexed to a bit under 8 feet on each side. The hip is maybe 3 to 4 feet above the ground. So, if you’re running along, you can only depress the wings about 40 degrees below the horizontal before they hit the ground. Ideally, you’d like to get a deeper stroke, and because these wings are so large, you can’t move them very quickly, so a faster stroke won’t work. Running helps you with takeoff speed, but that isn’t the problem.”

Instead, pterosaurs likely used their strong rear legs to jump upward, and then, once the ground clearance equaled the wing length, began to flap. Herons and egrets do the same, though they are considerably smaller than *Quetzalcoatlus*.

“If they could jump twice their hip height, to 8 feet, the wings would be able to clear the ground, and they could execute a deeper flight stroke,” Padian said. “This may be the best option for taking off, though it depends on sufficient power from the legs.”

He said that the forelimbs might have helped push the creature off the ground in the manner of vampire bats, but this would have required extraordinary strength of the extensor muscles of the forearm, which seems unlikely.

Given its habitat — inland marshes and open fields, much different from the West Texas desert today — the pterosaur’s most likely feeding strategy would resemble that of today’s egrets and herons, which are waders and stalkers with a varied diet. They sift the mud for crabs, worms and clams, but also snatch up small fish, insects, snakes and lizards.

“Some people said it was a carrion feeder, some people said it flew over the water and plucked fish like a pelican. Those things don’t work,” he said. “The jaws are very long and thin, tapering to a point. Wann used to call them chopsticks. And if you look at a heron or egret’s jaws, they’re the same — good for plucking lizards and other small game, but definitely not carcass-scavenging. It had no teeth.” *Quetzalcoatlus* could have been as skilled at stalking prey from the air as from land.

“This animal could raise its head and neck vertically, so as to

swallow the small prey it seized with its jaws. It could lower the great head far below the horizontal, so if it were cruising above dry land, it might have been able to swoop down and pluck an unsuspecting animal," Padian said. "Walking about on land, it could move its head and neck to an arc of 180 degrees, capable of full vision all around it."

Nearly 40 years ago, Padian teamed up with paleontologist Jean-Michel Mazin, who had discovered the pterosaur trackways in France, to describe the landing techniques of pterosaurs.

"The animal had to flap its wings to stall and slow its descent. And then it lands with its back feet and takes a little hop," Padian said. "And then it puts down its front feet, then it assumes a four-legged posture, straightens itself out and walks away."

The team's detailed reconstruction of the anatomy and behavior of *Quetzalcoatlus* was possible thanks to the excellent condition of the fossils, which were preserved in nearly their original three-dimensional shape, he said. This is rare for fossil animals and especially for pterosaurs, which have extremely thin bones that are usually crushed.

Padian admits that questions about *Quetzalcoatlus* and pterosaurs, in general, still remain, such as the shape of the wing membranes and where they were attached to the body. He pointed out that the legs were organized like those of birds and other dinosaurs, with the knees pointed forward, and that they put one foot in front of the other when walking. They could not have angled the legs sideways, however, like bats, which have unique hip joints that permit this.

Because of this, pterosaur legs would have been useless for extending the wings, which suggests that the wings were attached to the body only. Pterosaurs likely resembled birds in flight, with their legs tucked underneath.

All of the details will be online for the world to read and critique, thanks to Nathan Myhrvold, former chief technology officer of Microsoft Corp., who funded the various teams to prepare the monographs and paid for open access. The monograph was coedited by Matthew Brown, director of UT Austin's Vertebrate Paleontology Collections at the Jackson School of Geosciences.

"It's really exciting to get together all these people who have been involved with studying (*Quetzalcoatlus)* over the years, all these different aspects, from the history of discovery to the ancient environment of the animal to the study of what its anatomy was like and how many kinds of critters there were and how it walked and flew and took off, and so on," Padian said. "To put all these things in a single set of papers in a monograph is kind of one-stop-shopping for this animal. And we're really delighted to be able to make it open access, thanks to Nathan."

https://bit.ly/3pQ2uD5

Dogs Understand an Average of 89 Unique Words And Phrases, New Research Shows

The way dogs have come to understand the nuances of human language is incredibly impressive for an animal that doesn't speak words itself.

Carly Cassella

Just a fraction of a second after we start saying a word – like 'walk' or 'treat' – dogs can predict and respond to what we are trying to say. To some extent, they can even understand the tone of our voice.

While a dog's vocabulary is not nearly as large as our own, a new study suggests the average canine can consistently respond to 89 words or phrases. Nearly half of these are commands, like 'sit' or 'stay', but some general words, like 'wait', and nouns, like 'treat', are also understood. The most learned pooches of the lot were actually found to respond to over 200 specific words, which is roughly equivalent to the vocabulary of a two-year-old human child.

Obviously, a dog isn't speaking these words like a toddler would, but canines do seem to respond to certain words in a specific and

consistent way, which suggests they have some level of language comprehension.

The findings are based on an established vocabulary checklist, used by parents to assess a human infant's vocabulary. In this case, however, it was given to 165 owners of dogs, including canines from a range of breed types, ages and professions.

While breed type and work status (for instance, a police dog) seemed to have an impact on the size of a canine's vocabulary, its age and the qualities of its owner did not seem to influence the list.

"Thus," the authors write, "based on owner reports, dogs seem to vary greatly not only in the number but also in the kinds of words to which they purportedly respond."

Studies in the past have shown how dogs can learn to respond to an incredible number of human words if they undergo intense training. In 2004, for instance, researchers reported on a border collie named Rico who'd learned to retrieve over 200 items, including 'stuffed toys' and 'balls', just by hearing their names. In 2011, after three years of training, another border collie had acquired a toy vocabulary of over 1,000 words. Some particularly clever canines can even learn new words after hearing them only a handful of times. But what about your average household dog?

Using an online survey, the authors of the current study had dog owners report how their pet responded to 172 words and phrases.

There's always a chance with this type of research that the owners will overestimate their pet's understanding. But previous research on this specific vocabulary test among infants has found parents are better at understanding their child than a trained observer, so the same may apply to their pets, too.

What's more, by giving dog owners a fixed list of words to work through, this method ensures a pet owner doesn't forget to test some words, as might have happened in previous studies on canine vocabulary that came up with an average doggy lexicon about three times smaller.

Dog owners in the current survey were asked to rate their canine's response to certain words and phrases on a scale of 0 to five.

A score of 0 points meant their dog never responded specifically or consistently to a word or phrase. Whereas a score of five points meant the dog often did, even when the words were said in different locations, in different tones, and by different people.

Altogether, there were ten words or phrases specifically recognized by more than 90 percent of all the dogs. These common words and phrases included the dog's name, as well as 'sit', 'come', 'good girl/boy', 'down', 'stay', 'wait', 'no', 'ok', and 'leave it'.

In contrast, only a rare few dogs could consistently and specifically respond to phrases and words like 'wipe your feet', 'whisper', 'loud', 'antler', as well as names for the dog walker, the doggy daycare, the groomer, or the kennel.

When using the established vocabulary list, pet owners also had the opportunity to add more words and phrases. The owners that added the most commands, nouns or verbs tended to have professionally trained dogs, or dogs they believed were good at learning quickly.

Professional dogs, like those trained for the military, the police force, or search and rescue, had vocabularies 1.5 times larger than dogs without this career training.

The authors of the study didn't have enough dogs from each breed to figure out whether certain ones are better at learning words than others, but more general 'breed types', like herding dogs, toy companions, hounds, and terriers, did show significant variations in their word-learning abilities.

The owners of herding dogs and toy-companion dogs, for instance, tended to believe their dogs responded to more words than the owners of terriers, sporting-gun dogs, companion dogs, and other purebreds and mixed breed dogs.

Those are interesting findings, but because of the "exploratory

nature" of this research, the authors say firm conclusions about the ability of certain dog types to respond to human language is premature. Given how subjective it can be to interpret dog behavior and understanding, the findings of the current study come with limitations.

There's always a chance the dogs in the survey were incorporating human gestures and other contextual information into their understanding of certain words. What's more, because many of these dogs had received basic obedience training, there's the possibility a completely untrained dog would have a lower vocabulary than 89 words.

Still, the research is a good first step, and it highlights a potential way for scientists to measure dog responses to language in the future. With larger sample sizes, this tool could one day allow us to identify which words are most likely to be responded to by which dogs.

"With additional research, our tool could become an efficient, effective, and economical research instrument for mapping out some of their competences and perhaps help predict early the potential of individual dogs for various professions," the authors conclude.

The study was published in *Applied Animal Behaviour Science*.

https://bit.ly/3yx25tn

Chicxulub Impact Occurred during Northern Spring or Summer: Study

Chicxulub impact occurred during boreal spring/summer, shortly after the spawning season for fish and most continental species.

About 66 million years ago, a 10-km-wide asteroid crashed into Earth near the site of the small town of Chicxulub in what is now Mexico. The impact unleashed an incredible amount of climate-changing gases into the atmosphere, triggering a chain of events that led to the extinction of non-avian dinosaurs and 75% of life on the planet. According to an histological and histo-isotopic analysis of a unique impact-triggered assemblage of fossil fish from North Dakota, the United States, the Chicxulub impact occurred during boreal spring/summer, shortly after the spawning season for fish and most continental species.

“Time of year plays an important role in many biological functions such as reproduction, feeding strategies, host-parasite interactions, seasonal dormancy, and breeding patterns,” said Dr. Robert DePalma, a researcher with Charles E. Schmidt College of Science at Florida Atlantic University and the University of Manchester.

“Hence, it is no surprise that the time of year for a global-scale hazard can play a big role in how harshly it impacts life.”

“The seasonal timing of the Chicxulub impact has therefore been a critical question for the story of the end-Cretaceous extinction. Until now, the answer to that question has remained unclear.”

Dr. DePalma and colleagues examined the Tanis locality in southwestern North Dakota to understand the inner workings of the extinction event.

“This unique site in North Dakota had yielded a wealth of new and exciting information,” said Dr. Anton Oleinik, a researcher at Florida Atlantic University. “Field data collected at the site, after hard work that went into analyzing it, provided us with new incredibly detailed insight of not only what happened at the Cretaceous-Paleogene boundary, but also exactly when it happened.”

The unique structure and pattern of the growth lines in fossil fish bones from the Tanis site showed that all of the examined fish died during the spring-summer growth phase.

The isotopic analysis of the growth lines provided independent confirmation of this, showing a yearly oscillation that also terminated during the spring-summer growth.

The researchers further supported their findings by overlaying

multiple additional lines of evidence.

Examination of juvenile fossil fish was supported in part by cutting-edge synchrotron-rapid-scanning X-ray fluorescence (SRS-XRF), providing a novel way of seasonally dating the deposit.

Comparing the sizes of the youngest fish to modern growth rates enabled the scientists to predict how long after hatching the fish were buried. Comparing this to known modern spawning seasons enabled them to deduce what seasonal range was represented by the deposit at Tanis — spring to summer, just as indicated by the bones.

“The beauty of any great discovery such as this is that it is a chance to give back to the scientific community, and to the world,” Dr. DePalma said. “It not only answers important questions, but also sparks new minds to reach forward and achieve.”

The study was published in the journal *Scientific Reports*.

R.A. DePalma et al. 2021. Seasonal calibration of the end-cretaceous Chicxulub impact event. Sci Rep 11, 23704; doi: 10.1038/s41598-021-03232-9

https://bit.ly/3s0PSeU

When did scientists first warn humanity about climate change?

Scientists have known about climate change for a while.

By Patrick Pester

Climate change warnings are coming thick and fast from scientists; thousands have signed a paper stating that ignoring climate change would yield "untold suffering" for humanity, and more than 99% of scientific papers agree that humans are the cause. But climate change wasn't always on everyone's radar. So when did humans first become aware of climate change and the dangers it poses?

Scientists first began to worry about climate change toward the end of the 1950s, Spencer Weart, a historian and retired director of the Center for History of Physics at the American Institute of Physics in College Park, Maryland, told Live Science in an email. "It was just a possibility for the 21st century which seemed very far away, but seen as a danger that should be prepared for."

The scientific community began to unite for action on climate change in the 1980s, and the warnings have only escalated since. However, these recent warnings are just the tip of the melting iceberg; people's interest in how our activities affect the climate actually dates back thousands of years.

As far back as ancient Greece (1200 B.C. to A.D. 323), people debated whether draining swamps or cutting down forests might bring more or less rainfall to the region, according to Weart's Discovery of Global Warming website, which is hosted by the American Institute of Physics and shares the name with his book "The Discovery of Global Warming" (Harvard University Press, 2008).

The ancient Greek debates were among the first documented climate change discussions, but they focused only on local regions. It wasn't until a few millennia later, in 1896, that Swedish scientist Svante Arrhenius (1859-1927) became the first person to imagine that humanity could change the climate on a global scale, according to Weart. That's when Arrhenius published calculations in The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science showing that adding carbon dioxide to the atmosphere could warm the planet.

This work built on the research of other 19th-century scientists, such as Joseph Fourier (1768-1830), who hypothesized that Earth would be far cooler without an atmosphere, and John Tyndall (1820-1893) and Eunice Newton Foote (1819-1888), who separately demonstrated that carbon dioxide and water vapor trapped heat and suggested that an atmosphere could do the same, JSTOR Daily reported.

Arrhenius' climate change predictions were largely spot on. Human activities release carbon dioxide, methane and other greenhouse gases that trap radiation from the sun and hold them in the

atmosphere to increase temperature like a warming greenhouse, hence the term "greenhouse effect." However, Arrhenius' work was not widely read or accepted at the time, nor was it even intended to serve as a warning to humanity; it can be viewed as such only in hindsight. At the time, his work simply recognized the possibility of humans influencing the global climate and for a long time, people viewed warming as beneficial, according to Weart.

There was some coverage of fossil fuels affecting climate in the general media, according to a now-viral 1912 article first published in the magazine Popular Mechanics, USA Today reported. The article, which ran in a few newspapers in New Zealand and Australia later that year, recognized burning coal and releasing carbon dioxide could increase Earth's temperature, noting that "the effect may be considerable in a few centuries."

Why the 1950s?

The scientific opinion on climate change wouldn't begin to shift until two significant experiments some 60 years after Arrhenius' realization. The first, led by scientist Roger Revelle (1909-1991) in 1957 and published in the journal Tellus, found that the ocean will not absorb all of the carbon dioxide released in humanity's industrial fuel emissions and that carbon dioxide levels in the atmosphere could, therefore, rise significantly. Three years later, Charles Keeling (1928-2005) published a separate study in Tellus that detected an annual rise in carbon dioxide levels in Earth's atmosphere. With carbon dioxide levels known to affect the climate, scientists began to raise concerns about the impact human-related emissions could have on the world.

From there, more studies began highlighting climate change as a potential threat to species and ecosystems around the world. "Scientists first began in 1988 to insist that real action should be taken," Weart said. This occurred at the Toronto Conference on the Changing Atmosphere, where scientists and politicians from around the world gathered to address what was framed as a global threat to Earth's atmosphere, with calls to reduce emissions and knock-on effects such as acid rain.

"By the 1990s, most scientists thought action was necessary, but opposition from fossil fuel companies and ideologists opposed to any government action were effective in obscuring the facts and blocking action," Weart said. "Plus, normal human inertia and unwillingness to do anything without immediate benefits for oneself."

https://bit.ly/3EKY46J

Two Common Over-the-Counter Compounds Reduce COVID-19 Virus Replication by 99% in Early Testing

A pair of over-the-counter compounds has been found in preliminary tests to inhibit the virus that causes COVID-19, University of Florida Health researchers have found.

The combination includes diphenhydramine, an antihistamine used for allergy symptoms. When paired with lactoferrin, a protein found in cow and human milk, the compounds were found to hinder the SARS-CoV-2 virus during tests in monkey cells and human lung cells.

The findings by David A. Ostrov, Ph.D., an immunologist and associate professor in the UF College of Medicine's department of pathology, immunology and laboratory medicine and his colleagues, are published in the journal *Pathogens*.

"We found out why certain drugs are active against the virus that causes COVID-19. Then, we found an antiviral combination that can be effective, economical, and has a long history of safety," Ostrov said.

Due to his earlier research with colleagues at UF, Ostrov already knew diphenhydramine was potentially effective against the SARS-CoV-2 virus. The latest discovery has its roots in a routine meeting of scientists with the Global Virus Network's COVID-19 task force.

One researcher presented unpublished data on federally approved compounds that inhibit SARS-CoV-2 activity, including lactoferrin. Like diphenhydramine, lactoferrin is available without a prescription. Ostrov thought about pairing it with diphenhydramine and ran with the idea. In lab tests on human and monkey cells, the combination was particularly potent: Individually, the two compounds each inhibited SARS-CoV-2 virus replication by about 30%. Together, they reduced virus replication by 99%.

The findings, Ostrov said, are a first step in developing a formulation that could be used to accelerate COVID-19 recovery. It also raises the prospect of further study through an academic-corporate partnership for human clinical trials focused on COVID-19 prevention. Additional research into the compounds' effectiveness for COVID-19 prevention is already underway in mouse models.

To establish their findings, the research team focused on proteins expressed in human cells known as sigma receptors. In COVID-19 cases, the virus "hijacks" stress-response machinery, including sigma receptors, in order to replicate in the body. Interfering with that signaling appears to be the key to inhibiting the virus's potency. "We now know the detailed mechanism of how certain drugs inhibit SARS-CoV-2 infection," Ostrov said.

Data from the experiments show that a highly specific sigma receptor binding drug candidate (with pain relieving properties), and formulated combinations of over-the-counter products (such as diphenhydramine and lactoferrin) have the potential to inhibit virus infection and decrease recovery time from COVID-19, the researchers concluded.

While the findings are encouraging, Ostrov cautions against self-medicating with either diphenhydramine or lactoferrin as a COVID-19 prevention or treatment. The type of lactoferrin used in the research differs slightly from the type that is commonly available to consumers, he noted. Lactoferrin is commonly used as a supplement to treat stomach and intestinal ulcers, among other uses.

Reference: "Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells" by David A. Ostrov, Andrew P. Bluhm, Danmeng Li, Juveriya Qamar Khan, Megha Rohamare, Karthic Rajamanickam, Kalpana K. Bhanumathy, Jocelyne Lew, Darryl Falzarano, Franco J. Vizeacoumar, Joyce A. Wilson, Marco Mottinelli, Siva Rama Raju Kanumuri, Abhisheak Sharma, Christopher R. McCurdy and Michael H. Norris, 20 November 2021, Pathogens.
DOI: 10.3390/pathogens10111514
Scientists from UF's Emerging Pathogens Institute, College of Pharmacy and Clinical and Translational Science Institute, the University of Saskatchewan and the Saskatchewan Cancer Agency collaborated on the research.

https://bit.ly/3s4NjIS

Great News: An mRNA Flu Vaccine Just Delivered Positive Phase 1 Trial Results

Based on the same technology used in its successful COVID-19 vaccine

US biotech company Moderna on Friday announced promising data from an early-stage human trial of its mRNA flu shot, based on the same technology used in its successful COVID-19 vaccine.

The experimental flu shot was found to be safe, and successfully evoked high levels of antibodies in 180 people at all dosage levels, in both younger and older adults.

"Even before the COVID-19 pandemic, approximately 3 million people died each year due to respiratory infections, and many more are hospitalized or become ill as a result of these viruses," said Moderna CEO Stephane Bancel in a statement hailing the result.

Side effects were mild, and occurred more often in younger than older adults. The most common included pain and tenderness at the injection site, as well as headaches, muscle and joint aches, and tiredness.

The next stage of the trial, involving 500 people, began last month, and aims to firm up the right dosage level and compare the Moderna flu vaccine to already-licensed shots developed using

more traditional methods. Interim results are expected in early 2022. Later stages of the trial will assess the vaccine's efficacy.

The majority of current flu vaccines are based on inactivated viruses cultivated in chicken eggs. Virus strains have to be selected six to nine months before the vaccines are intended to be used, and their efficacy is approximately 40 to 60 percent.

Moderna and other vaccine manufacturers, including Sanofi, hope that mRNA technology – which provokes an immune response by delivering genetic molecules containing the code for key parts of a pathogen into human cells – can accelerate immunization development and production, and heighten efficacy.

Several mRNA molecules that encode for different strains can also be delivered in the same shot, a more efficient vaccination method that could lessen the load on public health systems.

Moderna's experimental flu shot is "quadrivalent", meaning it targets four strains of flu: A/H1N1, A/H3N2, B/Yamagata and B/Victoria – selected based on recommendations by the World Health Organization.

The company is also developing other flu shots that expand strain coverage further still, including a "pan-respiratory booster" to cover COVID-19, flu, and respiratory syncytial virus (RSV), a common virus that causes the cold but can be more serious for infants and elderly people.

https://bit.ly/3EQcFhj

We Just Got Closer to Understanding Why Asthma Might Protect From Brain Tumors

Neurologists in the United States think they have finally figured out why people with asthma seem to develop fewer brain tumors. The findings could one day help us develop better treatments for both conditions.

Carly Cassella

The curious connection between asthma and brain tumors first began popping up in global epidemiological research about 15 years ago, but without a proper mechanism linking the lung condition to the brain condition, some experts have dismissed the findings as random.

A new study now suggests the relationship may be real after all.

In 2015, neurologists published a study noting some children genetically prone to tumors along their optic brain pathway were not developing asthma at the same rate as you'd expect from the general population.

Further research in the lab found evidence these children's' tumors were being driven by an interaction between the optic nerve and some immune cells in the brain, known as T-cells and microglia.

Given that asthma is generally considered to be a T-cell mediated inflammatory disease, neurologists began to wonder if these immune cells were how the two conditions were connected.

To test the idea, researchers turned to mouse models. After genetically modifying the mice so that they were prone to optic nerve tumors, the authors induced asthma among litters at 4 and 6 weeks of age.

Curiously enough, the mice with induced asthma did not show evidence of brain tumors at 3 and 6 months. Meanwhile, those mice without asthma showed the expected development of brain cancer.

The findings suggest there's something about asthma that hurts the lungs while helping the brain, but what is that something?

A closer look at both groups of mice has indeed revealed a distinct difference in the behavior of their T-cells.

"Of course, we're not going to start inducing asthma in anyone; asthma can be a lethal disease," says neurologist David Gutmann from Washington University in St. Louis.

"But what if we could trick the T-cells into thinking they're asthma T-cells when they enter the brain, so they no longer support brain tumor formation and growth?"

In past research, when T-cells in the lungs of mice were stopped from producing a protein known as decorin, the animals showed less inflammation in their respiratory system.

In the current study, the mice with asthma also showed an increased expression of decorin in T-cells of their spleens, lymph nodes, and optic nerves. This matches results in humans with asthma, where the expression of decorin is similarly increased in the body's T-cells. In mice without asthma, however, decorin was not expressed nearly as much.

This suggests the T-cell-derived protein might not be great for the lungs, but it could have anti-carcinogenic effects in the brain.

Specifically, the authors found an increase of decorin along a mouse's optic nerve stopped the local T-cells from activating microglia, which are sentinel immune cells known to be associated with the growth of cancerous tumors.

It's therefore possible that treating the brain with decorin could potentially inhibit the accumulation of cancerous cells in humans, although further research will be needed to confirm these results among human children with asthma.

"We're also investigating the role of eczema and early-childhood infections, because they both involve T-cells," says Gutmann.

"As we understand this communication between T-cells and the cells that promote brain tumors better, we'll start finding more opportunities to develop clever therapeutics to intervene in the process." The study was published in *Nature Communications*.