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# Baby planets marinate in a life-giving cyanide 'soup,' analysis reveals

***The molecules needed for life are common in space.***

**By Adam Mann**

The universe may be teeming with the molecules needed for life, a new study finds. The results come from the most comprehensive maps ever made of the types and locations of chemicals in the gas and dust surrounding newborn stars.

Stars spring from enormous clouds of gas and dust, which collapse under their own weight into disk-like structures. The centers of these disks heat up through friction and increased pressure until they ignite into fusion-powered stars, while the surrounding matter slowly clumps together into ever-larger chunks.

"We have known for some time that planets form in disks around young stars and that these disks contain molecules of interest for predicting the future compositions of planets," Karin Öberg, an astrochemist at Harvard University in Cambridge, Massachusetts, told Live Science.

A few years ago, Öberg and her colleagues decided to use the Atacama Large Millimeter/submillimeter Array (ALMA), a telescope in Chile that sees in the radio part of the electromagnetic spectrum, as a part of the Molecules with ALMA at Planet-forming Scales (MAPS) program. Because of their shapes and the bonds inside them, different chemicals vibrate in unique ways, producing telltale signatures that ALMA can capture, according to ALMA scientists.

The team looked at five protoplanetary disks, all between 1 million and 10 million years old, within a few hundred light-years of Earth. "That means they are in an actively planet-forming epoch," Öberg said.

MAPS determines not only the specific molecules in protoplanetary disks but also their locations. "Planets can form at many different distances from the star," Öberg said, so it's important to know what chemicals are available in each location to build these future planets. An astounding 20 papers from this extensive mapping project are being published in a special future issue of The Astrophysical Journal Supplement Series; the first of these papers was made available on the preprint server arXiv on Sept. 15.

"What's so awesome is that there are several pieces rather than one big answer," Öberg said. "I think all 20 papers provide some different piece of the puzzle."

One of the most exciting findings for her was the abundance and distribution of a class of molecules known as cyanides. The simplest member of this family, hydrogen cyanide, is typically considered a poison, though many theories for the origin of life include a major role for this chemical class, she said.

"Seeing them in large abundance means planets are forming in the kind of soup we'd like to see" in order to fuel the emergence of life, Öberg added. Cyanides also tended to be concentrated toward the inner parts and midplanes of the disks studied by MAPS — exactly where planets are expected to arise, she said.

Such molecules could form only in a low-oxygen environment with lots of carbon, Öberg added. This suggests that planets will be born with carbon-rich atmospheres, another point in favor of living things, since carbon is the basis of organic chemistry.

The results show that at least some of the organic building blocks of life are probably available in other stellar systems, but that doesn't necessarily make it more likely for humanity to find living organisms elsewhere. "It's promising from an origin-of-life point of view," Öberg said. "But there's still a lot of work to do."

Living creatures would have needed a certain subset of chemicals in specific amounts in order to arise spontaneously, and scientists have yet to agree on what that recipe for life was.

There has been a lot of past effort into understanding the chemistry in the clouds that give rise to stars, as well as into analyzing the molecules in asteroids and comets, which can contain information about later periods of planetary formation, said Kathrin Altwegg, a planetary scientist at the University of Bern in Switzerland who was not involved in the new work.

"But there was one stage missing," Altwegg told Live Science — the stage that determined the chemistry in protoplanetary disks, and the results from this project are now helping to fill in unexplored details.

The findings also imply that a great deal of complex chemical formation already takes place prior to the birth of stars and planets, suggesting that these molecules come from interstellar clouds and are, therefore, widespread in space, she added.

***https://wb.md/3mEMhiF***

## Pfizer COVID Vaccine Antibodies May Disappear in 7 Months, Study Says

***Antibody levels may wane after 7 months for people who got the Pfizer-BioNTech vaccine, according to a new study published on the bioRxiv preprint server.***

**Carolyn Crist**

In the study, which hasn't yet been peer-reviewed or formally published in a medical journal, researchers analyzed blood samples from 46 healthy young or middle-aged adults after receiving two doses, and then 6 months after the second dose.

"Our study shows vaccination with the Pfizer-BioNTech vaccine induces high levels of neutralizing antibodies against the original vaccine strain, but these levels drop by nearly 10-fold by 7 months," the researchers told Reuters.

In about half of the adults, neutralizing antibodies were undetectable at 6 months after the second dose, particularly against coronavirus variants such as Delta, Beta, and Mu.

Neutralizing antibodies only make up part of the body's immune defense against the virus, Reuters noted, but they are still "critically important" in protecting against coronavirus infections.

"These findings suggest that administering a booster dose at around 6 to 7 months following the initial immunization will likely enhance protection," the study authors wrote.

BioNTech said a new vaccine formula will likely be needed by mid-2022 to protect against future mutations of the virus, according to the *Financial Times.*

"This year, [a different vaccine] is completely unneeded, but by mid-next year, it could be a different situation," Ugur Sahin, MD, co-founder and CEO of BioNTech, told the news outlet.

Current variants, namely the Delta variant, are more contagious than the original coronavirus strain but not different enough to evade current vaccines, he said. But new strains may be able to evade boosters.

"This virus will stay, and the virus will further adapt," Sahin said. "This is a continuous evolution, and that evolution has just started."

***Sources:***

*BioRxiv: "Durability of immune responses to the BNT162b2 mRNA vaccine."*
*Reuters: "Delta increases COVID-19 risks for pregnant women; Pfizer/BioNTech vaccine antibodies gone by 7 months for many."*
*Financial Times: "BioNTech chief predicts need for updated Covid vaccines next year."*

***https://nyti.ms/3oDVwlI***

## Losing Your Hair? You Might Blame the Great Stem Cell Escape.

***By observing mouse hair follicles, scientists discovered an unexpected mechanism of aging.***

**By Gina Kolata**

“If I didn’t see it with my own eyes I wouldn't believe it,” one said.

Every person, every mouse, every dog, has one unmistakable sign of aging: hair loss. But why does that happen?

Rui Yi, a professor of pathology at Northwestern University, set out

to answer the question.

A generally accepted hypothesis about stem cells says they replenish tissues and organs, including hair, but they will eventually be exhausted and then die in place. This process is seen as an integral part of aging. Instead Dr. Yi and his colleagues made a surprising discovery that, at least in the hair of aging animals, stem cells escape from the structures that house them.

“It’s a new way of thinking about aging,” said Dr. Cheng-Ming Chuong, a skin cell researcher and professor of pathology at the University of Southern California, who was not involved in Dr. Yi’s study, which was published on Monday in the journal Nature Aging. The study also identifies two genes involved in the aging of hair, opening up new possibilities for stopping the process by preventing stem cells from escaping.

Charles K.F. Chan, a stem cell researcher at Stanford University, called the paper “very important,” noting that “in science, everything about aging seems so complicated we don’t know where to start.” By showing a pathway and a mechanism for explaining aging hair, Dr. Yi and colleagues may have provided a toehold.

Stem cells play a crucial role in the growth of hair in mice and in humans. Hair follicles, the tunnel-shaped miniature organs from which hairs grow, go through cyclical periods of growth in which a population of stem cells living in a specialized region called the bulge divide and become rapidly growing hair cells.

Sarah Millar, director of the Black Family Stem Cell Institute at the Icahn School of Medicine at Mount Sinai, who was not involved in Dr. Yi’s paper, explained that those cells give rise to the hair shaft and its sheath. Then, after a period of time, which is short for human body hair and much longer for hair on a person’s head, the follicle becomes inactive and its lower part degenerates. The hair shaft stops growing and is shed, only to be replaced by a new strand of hair as the cycle repeats.

But while the rest of the follicle dies, a collection of stem cells remains in the bulge, ready to start turning into hair cells to grow a new strand of hair.

Dr. Yi, like most scientists, had assumed that with age the stem cells died in a process known as stem cell exhaustion. He expected that the death of a hair follicle’s stem cells meant that the hair would turn white and, when enough stem cells were lost, the strand of hair would die. But this hypothesis had not been fully tested.

Together with a graduate student, Chi Zhang, Dr. Yi decided that to understand the aging process in hair, he needed to watch individual strands of hair as they grew and aged.

Ordinarily, researchers who study aging take chunks of tissue from animals of different ages and examine the changes. There are two drawbacks to this approach, Dr. Yi said. First, the tissue is already dead. And it is not clear what led to the changes that are observed or what will come after them.

He decided his team would use a different method. They watched the growth of individual hair follicles in the ears of mice using a long wavelength laser that can penetrate deep into tissue. They labeled hair follicles with a green fluorescent protein, anesthetized the animals so they did not move, put their ear under the microscope and went back again and again to watch what was happening to the same hair follicle.

What they saw was a surprise: When the animals started to grow old and gray and lose their hair, their stem cells started to escape their little homes in the bulge. The cells changed their shapes from round to amoeba-like and squeezed out of tiny holes in the follicle. Then they recovered their normal shapes and darted away.

Sometimes, the escaping stem cells leapt long distances, in cellular terms, from the niche where they lived.

“If I did not see it for myself I would not have believed it,” Dr. Yi said. “It’s almost crazy in my mind.”

The stem cells then vanished, perhaps consumed by the immune system.

Dr. Chan compared an animal's body to a car. “If you run it long enough and don’t replace parts, things wear out,” he said. In the body, stem cells are like a mechanic, providing replacement parts, and in some organs like hair, blood and bone, the replacement is continual. But with hair, it now looks as if the mechanic — the stem cells — simply walks off the job one day.

But why? Dr. Yi and his colleagues’ next step was to ask if genes are controlling the process. They discovered two — FOXC1 and NFATC1 — that were less active in older hair follicle cells. Their role was to imprison stem cells in the bulge. So the researchers bred mice that lacked those genes to see if they were the master controllers.

By the time the mice were 4 to 5 months old, they started losing hair. By age 16 months, when the animals were middle-aged, they looked ancient: They had lost a lot of hair and the sparse strands remaining were gray.

Now the researchers want to save the hair stem cells in aging mice.

This story of the discovery of a completely unexpected natural process makes Dr. Chuong wonder what remains to be learned about living creatures. “Nature has endless surprises waiting for us,” he said. “You can see fantastic things.”

***https://bbc.in/302r3mV***

## Brain implant may lift most severe depression

***An electrical implant that sits in the skull and is wired to the brain can detect and treat severe depression, US scientists believe after promising results with a first patient.***

**By Michelle Roberts**

Sarah, who is 36, had the device fitted more than a year ago and says it has turned her life around. The matchbox-sized pack in her head is always "on" but only delivers an impulse when it senses she may need it.

The experimental study is described in Nature Medicine journal. The researchers, from University of California, San Francisco, stress it is too soon to say if it might help other patients, like Sarah, with hard-to-treat depression, but they are hopeful and plan more trials.

***Prof Katherine Scangos checking Sarah's device and progress*** **Maurice Ramirez, UCSF 2021**

### Depression circuits

Sarah is the first person to have had the experimental therapy.

She'd had a succession of failed treatments, including anti-depressants and electroconvulsive therapy in recent years.

The surgery may sound daunting, but Sarah said the prospect of gaining "any kind of relief" was better than the darkness she had been experiencing. "I had exhausted all possible treatment options. "My daily life had become so restricted. I felt tortured each day. I barely moved or did anything."

The surgery involved drilling small holes in her skull to fit the wires that would monitor and stimulate her brain. The box, containing the battery and the pulse generator, was tucked into the bone, beneath her scalp and hair. The procedure took a full working day and was done under general anaesthetic, meaning Sarah was unconscious throughout.

Sarah says when she woke, up she felt euphoric. "When the implant was first turned on, my life took an immediate upward turn. My life was pleasant again. "Within a few weeks, the suicidal thoughts disappeared. "When I was in the depths of depression all I saw is what was ugly." A year on, Sarah remains well, with no side-effects. "The device has kept my depression at bay, allowing me to return to

my best self and rebuild a life worth living."
She can't feel the device as it fires, but says: "I could probably tell you within 15 minutes that it has gone off because of a sense of alertness and energy or the positivity I will feel."

**How it works**

Researcher Dr Katherine Scangos, who is a psychiatrist at the university, said the innovation was made possible by locating the "depression circuits" in Sarah's brain.
"We found one location, which is an area called the ventral striatum, where stimulation consistently eliminated her feelings of depression.
"And we also found a brain activity area in the amygdala that could predict when her symptoms were most severe."
The scientists say a lot more research is needed to test the experimental therapy and determine if it can help more people with severe depression, and perhaps other conditions too.

**Personalised treatment**

Dr Scangos, who has enrolled two other patients in the trial and hopes to recruit nine more, said: "We need to look at how these circuits vary across patients and repeat this work multiple times.
"And we need to see whether an individual's biomarker or brain circuit changes over time as the treatment continues. "We didn't know if we were going to be able to treat her depression at all because it was so severe. "So in that sense we are really excited about this. It's so needed in the field right now."
Dr Edward Chang, the neurosurgeon who fitted the device, said: "To be clear, this is not a demonstration of efficacy of this approach.
"It's really just the first demonstration of this working in someone and we have a lot of work ahead of us as a field to validate these results to see if this actually is something that will be enduring as a treatment option."
Prof Jonathan Roiser, a neuroscience expert at University College London in the UK, said: "Although this kind of highly invasive surgical procedure would only ever be used in the most severe patients with intractable symptoms, it is an exciting step forward due to the bespoke nature of the stimulation.
"It is likely that if trialled in other patients, different recording and stimulation sites would be required, as the precise brain circuitry underlying symptoms probably varies between individuals.
"As there was only one patient and no control condition, it remains to be seen whether these promising results hold in clinical trials."

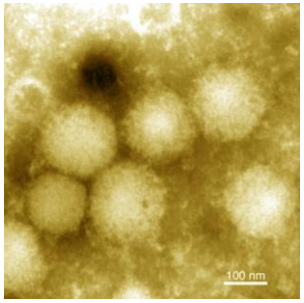
***https://bit.ly/3ajaMMe***

## New Tick-Borne Virus Discovered in Japan

***Scientists have isolated a new orthonairovirus from two patients showing acute febrile illness with thrombocytopenia and leukopenia after tick bite in Hokkaido, Japan.***

**by Enrico de Lazaro**

Orthonairoviruses are tick-borne viruses in the genus *Orthonairovirus*, the family Nairoviridae. They cause sometimes fatal febrile illnesses in humans and other animals.
Of 15 species within the genus, four species comprise known human pathogens: Crimean-Congo hemorrhagic fever virus, Nairobi sheep disease virus, Dugbe virus, and Kasokero virus.




***Transmission electron microscopy of YEZV particles negatively stained with 2% phosphotungstic acid.*** **Image credit: Kodama et al., doi: 10.1038/s41467-021-25857-0.**

The newly-discovered orthonairovirus, named Yezo virus (YEZV), is the causative agent of an acute febrile illness characterized by thrombocytopenia, leukopenia, and elevation of liver enzymes and ferritin.
“At least seven people have been infected with this new virus in Japan since 2014,” said Dr. Keita Matsuno, a virologist in the International Institute for Zoonosis Control at Hokkaido University.

The Yezo virus was discovered after a 41-year-old man was admitted to the hospital in 2019 with fever and leg pain after being bitten by an arthropod believed to be a tick.

"In mid-May 2019, he visited a forest area near Sapporo for approximately 4 hours," the researchers said.

"The next day, he noticed and removed an arthropod attached to his right abdomen. Four days after visiting the forest, he had a fever over 39 degrees Celsius, followed by gait disturbance and leg pain."

"After the fever continued for 4 days, he was admitted to our hospital with a temperature of 38.9 degrees Celsius. On admission, a review of systems was negative except for a fever, appetite loss, and bilateral lower extremity pain."

The patient was treated and discharged after two weeks, but tests showed he had not been infected with any known tick-borne viruses.

A second patient showed up with similar symptoms after a tick bite the following year. "The patient was a 59-year-old previously healthy male with no remarkable medical history living in Sapporo, Hokkaido," the scientists said.

"In mid-July 2020, he hiked on a mountain near Sapporo. During the hike, he received a bite on his lower leg from an unidentified arthropod that remained attached for at least 30 min.."

"He remained in his usual state of health until 9 days after the hike when he lost his appetite and then, developed a fever of 37.4 degrees Celsius on 17 days after the hike."

"Following two visits to different hospitals on days 3 and 4 after the onset of fever, where he was found to have a fever (38.5 degrees Celsius on day 3) with leukopenia and thrombocytopenia, he visited our hospital on day 5 post-onset of fever."

The genetic analysis of viruses isolated from blood samples of the two patients revealed a new type of orthonairovirus, which is most closely related to Sulina virus and Tamdy virus, detected in Romania and Uzbekistan, respectively.

To determine the likely source of the virus, the team screened samples collected from wild animals in the area between 2010 and 2020. They found antibodies for the virus in Hokkaido sika deer and raccoons. They also found the virus RNA in three major species of ticks in Hokkaido.

"The Yezo virus seems to have established its distribution in Hokkaido, and it is highly likely that the virus causes the illness when it is transmitted to humans from animals via ticks," Dr. Matsuno said.

*The team's paper was published in the journal Nature Communications.*
*F. Kodama et al. 2021. A novel nairovirus associated with acute febrile illness in Hokkaido, Japan. Nat Commun 12, 5539; doi: 10.1038/s41467-021-25857-0*

***https://bit.ly/3ap9oHW***

## Late Persistence of Human Ancestors at the Margins of the Monsoon Zone in India

***Revealing the presence of Acheulean populations until about 177,000 years ago***

The longest lasting tool-making tradition in prehistory, known as the Acheulean, appears more than 1.5 million years ago in Africa and 1.2 million years ago in India, and mainly consists of stone handaxes and cleavers (Figure 1). New research led by the Max Planck Institute for the Science of Human History has re-examined a key Acheulean site at the margins of the monsoon zone in the Thar Desert, Rajasthan, revealing the presence of Acheulean populations until about 177,000 years ago, shortly before the earliest expansions of *Homo sapiens* across Asia.

***A handaxe from the Thar Desert, where Acheulean populations persisted until at least 177 thousand years ago.*** **Credit: Jimbob Blinkhorn**

The timing and route of the earliest expansions of our own species across Asia have been the focus of considerable debate but a growing body of evidence indicates *Homo sapiens* interacted with

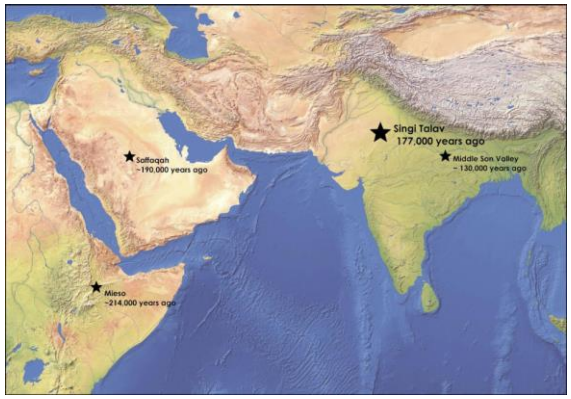
numerous populations of our closest evolutionary cousins. Identifying where these different populations met is critical to revealing the human and cultural landscape encountered by the earliest members of our species to expand beyond Africa. Although fossils of ancient human populations are extremely rare in South Asia, changes in the stone tool kits they made, used, and left behind can help resolve when and where these encounters may have occurred.

**The youngest Acheulean in western India**

In a paper published in *Scientific Reports*, an international team of researchers led by the Max Planck Institute for the Science of Human History report the relatively recent occupation of the site of Singi Talav (Rajasthan, India) by Acheulean populations up to 177,000 years ago (Figure 2). The site was once thought to be amongst the oldest Acheulean sites in India, but now appears to be one of the youngest. Indeed, these dates show the persistence of Acheulean populations in the Thar Desert after their disappearance in eastern Africa around 214,000 years ago and Arabia 190,000 years ago. This result supports the late persistence of Acheulean populations in India, where previous research has shown their presence as recently as 130,000 years ago.

The site of Singi Talav, set on a lakeside close to the modern town of Didwana at the edge of the Thar Desert, was first excavated in the early 1980's, revealing multiple stone tool assemblages (Figure 3). The largest assemblage shows a focus on the production of stone handaxes and cleavers that are typical of the Acheulean. However, the techniques needed to accurately date these assemblages were not available at the time of their discovery. Since then, a range of sites have been examined that constrain the chronology of Acheulean occupations in India, but the ecological settings of the sites remains poorly known.

"The lakeside setting has ideal preservation conditions for an archaeological site, enabling us to return 30 years after the first excavation and readily re-identify the main occupation horizons again," says Dr. Jimbob Blinkhorn of the Max Planck Institute for the Science of Human History, the lead author of the study. "We've applied a range of modern methods to re-examine this critical site, including new approaches to directly date the occupation horizons and to reveal the vegetation in the landscape that Acheulean populations inhabited."




***Acheulean map.*** **Credit: Max Planck Institute**

The researchers used luminescence methods to directly date the sediment horizons occupied by ancient human populations. These methods rely on the ability of minerals like quartz and feldspar to store and release energy induced by natural radioactivity, allowing scientists to determine the last time sediments were exposed to light. "Ours is the first study to directly date the occupation horizons at Singi Talav, enabling us to understand both when ancient humans lived here and created the stone tool assemblages, and how these occupations compare with other sites across the region," adds Dr. Julie Durcan of the University of Oxford.

**At the margins of the monsoon**

The Thar Desert sits at the western edge of the modern Indian summer monsoon system, and its habitability to ancient human populations likely fluctuated significantly. The researchers examined plant microfossils, known as phytoliths, as well as features of soil geochemistry to reveal the ecology of the site at the time the Acheulean toolkits were produced.

"This is the first time the ecology of an Acheulean site in India has been studied using these methods, revealing the broader character of the landscape that these populations inhabited," says Prof Hema Achyuthan of Anna University, Chennai, who also participated in the original excavations at the site. "The results from the two methods we applied complement each other to reveal a landscape rich in the types of grasses that flourish during periods with enhanced summer monsoons."

With this data, the study illuminates the environmental conditions that allowed Acheulean populations to thrive at the margins of the monsoon in the Thar Desert until at least 177,000 years ago.

"This supports evidence from across the region indicating that India hosted the youngest populations using Acheulean toolkits across the world," adds Blinkhorn. "Critically, the late persistence of the Acheulean at Singi Talav and elsewhere in India directly precedes evidence for the appearance of our own species, *Homo sapiens*, as they expanded across Asia."

The Thar Desert likely presented a key ecological frontier for expanding populations of Homo sapiens moving eastwards as they first met the Indian monsoon system. The results of this study suggest that this may have also been a demographic and behavioral frontier — a potential zone in which *Homo sapiens* encountered another, closely related, human population.

*Reference: "Constraining the chronology and ecology of Late Acheulean and Middle Palaeolithic occupations at the margins of the monsoon" 5 October 2021, Scientific Reports. DOI: 10.1038/s41598-021-98897-7*

***https://bit.ly/3Aofymt***

## Overload of Inflammatory Molecules "Trapped" in Micro Blood Clots May Cause Long COVID Symptoms

***First evidence of inflammatory micro clots in blood of individuals suffering from Long COVID:***

This may be the cause of some of the lingering symptoms experienced by individuals with Long COVID.

New research indicates that an overload of various inflammatory molecules, literally "trapped" inside insoluble microscopic blood clots (micro clots), might be the cause of some of the lingering symptoms experienced by individuals with Long COVID.

This unexpected finding was made by Prof Resia Pretorius, a researcher in the Department of Physiological Science at Stellenbosch University (SU), when she started looking at micro clots and their molecular content in blood samples from individuals with Long COVID. The findings have since been peer-reviewed and published in the journal *Cardiovascular Diabetology* in August 2021.

"We found high levels of various inflammatory molecules trapped in micro clots present in the blood of individuals with Long COVID. Some of the trapped molecules contain clotting proteins such as fibrinogen, as well as alpha(2)-antiplasmin," Prof Pretorius explains.

Alpha(2)-antiplasmin is a molecule that prevents the breakdown of blood clots, while fibrinogen is the main clotting protein. Under normal conditions the body's plasmin-antiplasmin system maintains a fine balance between blood clotting (the process by which blood thickens and coagulate to prevent blood loss after an injury) and fibrinolysis (the process of breaking down the fibrin in the coagulated blood to prevent blood clots from forming).

With high levels of alpha(2)-antiplasmin in the blood of COVID-19 patients and individuals suffering from Long COVID, the body's ability to break down the clots are significantly inhibited.

The insolubility of the micro clots became apparent when Dr Maré Vlok, a senior analyst in the Mass Spectrometry Unit at SU's Central Analytical Facilities, noted that the blood plasma samples from individuals with acute COVID and Long COVID continued to deposit insoluble pellets at the bottom of the tubes after dilution (a process called trypsinization).

He alerted Prof Pretorius to this observation and she investigated it further. They are now the first research group to have reported on finding micro clots in the blood samples from individuals with Long COVID, using fluorescence microscopy and proteomics analysis, thereby solving yet another puzzle associated with the disease.

Of particular interest is the simultaneous presence of persistent anomalous micro clots and a pathological fibrinolytic system," they write in the research paper. This implies that the plasmin and antiplasmin balance may be central to pathologies in Long COVID, and provides further evidence that COVID-19, and now Long COVID, have significant cardiovascular and clotting pathologies.

Further research is recommended into a regime of therapies to support clotting and fibrinolytic system function in individuals with lingering Long COVID symptoms.

Working with vascular internist Dr. Jaco Laubscher from Mediclinic Stellenbosch (a co-author on the article), they now plan to perform the same analysis on a larger sample of patients. To date they have collected blood from one hundred Long COVID individuals who participated in the Long COVID registry which launched in May 2021, as well as from 30 healthy individuals. The research is funded by the Long COVID Research Charitable Trust, a trust established with an initial donation made by Mr. Koos Pretorius from ENSafrica. It is intended that this trust will be used as a vehicle to raise further funds for research into the causes and effective treatment of people suffering from Long COVID.

*Reference: "Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin" by Etheresia Pretorius, Mare Vlok, Chantelle Venter, Johannes A. Bezuidenhout, Gert Jacobus Laubscher, Janami Steenkamp and Douglas B. Kell, 23 August 2021, Cardiovascular Diabetology. DOI: 10.1186/s12933-021-01359-7*

***https://bit.ly/2Yugj07***

## Scientists Developed an Experimental Vaccine Against Rheumatoid Arthritis – "Totally Disappeared"

***The protein-based vaccine shows significant promise in preventing rheumatoid arthritis and improving bone quality — suggesting long-term benefits following immunization.***

Researchers at The University of Toledo have developed an experimental vaccine that shows significant promise in preventing rheumatoid arthritis, a painful autoimmune disease that cannot currently be cured.

"Much to our happy surprise, the rheumatoid arthritis totally disappeared in animals that received a vaccine." — *Dr. Ritu Chakravarti*

The findings, detailed in a paper published in the journal *Proceedings of the National Academy of Sciences*, represent a major breakthrough in the study of rheumatoid arthritis and autoimmune diseases in general.

One of the most common autoimmune diseases, rheumatoid arthritis occurs when the body's immune system attacks and breaks down healthy tissue — most notably the lining of joints in the hands, wrists, ankles, and knees.

Some estimates suggest rheumatoid arthritis affects as much as 1% of the global population.

"In spite of its high prevalence, there is no cure and we don't entirely know what brings it on. This is true of nearly all autoimmune diseases, which makes treating or preventing them so difficult," said Dr. Ritu Chakravarti, an assistant professor in the UToledo College of Medicine and Life Sciences and the paper's lead author. "If we can successfully get this vaccine into the clinic, it would be revolutionary."

Chakravarti has for years studied a protein called 14-3-3 zeta and its role in immune pathologies, including aortic aneurysms and

interleukin-17— a cytokine associated with autoimmune diseases. Based on their prior work, the research group was focused on the protein as a potential trigger for rheumatoid arthritis.

Instead, they found the opposite.

Rather than preventing rheumatoid arthritis, researchers discovered that removing the protein through gene-editing technology caused severe early onset arthritis in animal models.

Working under a new theory that the 14-3-3 zeta protein protects against rheumatoid arthritis, the team developed a protein-based vaccine using purified 14-3-3 zeta protein grown in a bacterial cell.

They found the vaccine promoted a strong and immediate — but long-lasting — response from the body's innate immune system, providing protection against the disease.

"Much to our happy surprise, the rheumatoid arthritis totally disappeared in animals that received a vaccine," Chakravarti said. "Sometimes there is no better way than serendipity. We happened to hit a wrong result, but it turned out to be the best result. Those kinds of scientific discoveries are very important in this field."

In addition to suppressing the development of arthritis, the vaccine also significantly improved bone quality — a finding that suggests there should be long-term benefits following immunization.

Currently, rheumatoid arthritis is treated primarily with corticosteroids, broad scale immunosuppressive drugs or newer, more targeted biologics that target a specific inflammatory process.

While those therapeutics can alleviate pain and slow the progression of the disease, they also can make patients more vulnerable to infection and, in the case of biologics, can be costly.

"We have not made any really big discoveries toward treating or preventing rheumatoid arthritis in many years," Chakravarti said. "Our approach is completely different. This is a vaccine-based strategy based on a novel target that we hope can treat or prevent rheumatoid arthritis. The potential here is huge."

Researchers have filed for a patent on their discovery and are seeking pharmaceutical industry partners to support safety and toxicity studies in hopes of establishing a preclinical trial.

*Reference: "14-3-3ζ: A suppressor of inflammatory arthritis" by Joshua Kim, Krista Chun, Jenna McGowan, Youjie Zhang, Piotr J. Czernik, Blair Mell, Bina Joe, Saurabh Chattopadhyay, Joseph Holoshitz and Ritu Chakravarti, 24 August 2021, Proceedings of the National Academy of Sciences.DOI: 10.1073/pnas.2025257118*

***https://bit.ly/3DlVinb***

## Adorable, bloodsucking sea parasite looks just like sushi

***The isopod was discovered off the coast of Japan and is a new aquarium superstar.***

**By Brandon Specktor**

Do not adjust your screen, and do not reach for the soy sauce. What you see before you is a real, living, breathing marine animal currently on display in a Japanese aquarium — a creature that just happens to look exactly like a piece of salmon sushi.

***The sushi-shaped isopod is a crustacean like no other.*** **(Image credit: Aquamarine Fukushima)**

This snack of a sea creature is one of the most popular residents of Aquamarine Fukushima, a large aquarium on the east coast of Japan. In a Twitter post, aquarium staff identified the creature as an isopod — an order of long, flat, armor-plated crustaceans that are plentiful on land and in the sea. The nigiri-shaped superstar likely belongs to the genus *Rocinela*, which includes more than 40 species, aquarium caretaker Mai Hibino told Vice.

While many isopods eat dead or decaying animals, *Rocinela* isopods tend to be parasites that carve out cozy homes on the backs or among the internal organs of other sea creatures. Most members of the genus appear dull and brown, but it's possible that

Fukushima's famed sushi isopod may have taken more than just a meal from one of its former hosts, Hibino said.

"Because they're parasitic, we think maybe the color of the fish it was feeding on transferred [to the isopod]," Hibino told Vice.

Fishers caught the peculiar isopod in a net near the coastal town of Rausu on Hokkaido, Japan's northernmost island. The creature was captured at a depth of 2,600 to 4,000 feet (800 to 1,200 meters) and seemed to have a full belly upon discovery, Hibino said. Sadly, there's no way of knowing exactly what the isopod fed on to achieve its raw-fish complexion. Measuring just 1 inch (3 centimeters) in length, the isopod could have easily stowed away on any number of larger sea creatures, the aquarium said.

This strangeness is par for the course for isopods; more than 10,000 species have been described to date, with diets, habitats and sizes ranging wildly. For instance, scientists writing in the journal ZooKeys in 2020 described the largest isopod ever detected: a puppy-size chonker whose sinister, domed shell earned it the nickname "Darth Vader of the seas." That's one crustacean we wouldn't want to invite to dinner.

***https://go.nature.com/3DuAwSn***

## An abandoned antibiotic makes a comeback to fight a common illness

***Hygromycin A doesn't work well against most bacteria, but it shines as a treatment for Lyme disease.***

The bacterial infection called Lyme disease is difficult to treat, can inflict lasting nerve damage and affects almost 500,000 people annually in the United States alone. Now tests in mice show that an antibiotic that had been sitting on the shelf for decades blocks the bacterium that causes Lyme — without the serious side effects of current treatments[1].

Lyme, which is spread by ticks, is currently treated with 'broad spectrum' antibiotics. These impair a wide range of microorganisms, including beneficial residents of the gut, and promote the growth of antibiotic-resistant bacteria.

Many existing antibiotics are compounds produced by soil bacteria. To identify one that would target *Borreliella burgdorferi*, which causes Lyme, Kim Lewis at Northeastern University in Boston, Massachusetts, and his colleagues screened hundreds of strains of soil bacteria. This led them to rediscover the bacterial compound hygromycin A. In lab dishes, this molecule prevented the growth of bacteria related to *B. burgdorferi*, but did little damage to other microbes.

In mice, the antibiotic cleared *B. burgdorferi* infections and did not substantially harm the animals' gut bacteria. The authors suggest that, thanks to this specificity, the compound could both treat and prevent Lyme disease.

*Nature* ***598***, *238 (2021) doi: https://doi.org/10.1038/d41586-021-02716-y*

***References 1.*** *Leimer, N. et al. Cell https://www.sciencedirect.com/science/article/pii/S0092867421010588?via%3Dihub*

***https://bit.ly/3mD8ZYq***

## In landmark decision, WHO greenlights rollout in Africa of the first malaria vaccine

***RTS,S is safe and effective, panel concludes—but questions remain***

**By Gretchen Vogel**

In a momentous and long-awaited decision, the World Health Organization (WHO) today recommended the wide rollout of a malaria vaccine to protect children in Africa. That opens the way for countries to decide how to use the vaccine, the first ever to be approved for a parasitic disease, as part of their malaria control programs. It also allows funders to pledge financial support for ramping up vaccine production and distribution.

Data from a pilot rollout involving more than 800,000 children in three African countries convinced a panel of malaria and vaccine

experts advising WHO that the vaccine, called RTS,S, or Mosquirix, is safe, and despite its modest efficacy should be offered widely to children in African regions that have moderate or high malaria transmission. (The vaccine only targets the malaria parasite *Plasmodium falciparum*, which is prevalent in Africa.)

The announcement, capping a decadeslong quest for a malaria vaccine, "is an historic moment in the fight against malaria," says Corine Karema, a member of WHO's advisory group for the pilot rollout and former director of Rwanda's National Malaria Control Programme.

But not everybody is convinced the shots are the best way to spend scarce public health dollars in Africa. The vaccine is far from perfect: It requires four doses and only provides roughly 30% protection against severe malaria in children. Initial studies also raised possible questions about its safety, and some researchers caution that studies so far may have missed some of its downsides.

Malaria kills an estimated 260,000 children under age 5 in Africa each year, a number that was falling rapidly between 2004 and 2015 but has since leveled off. "We need new tools to get malaria under control," WHO Director-General Tedros Adhanom Ghebreyesus said at a press conference today.

First developed in the 1980s, RTS,S contains a piece of a *P. falciparum* protein linked to a protein from the hepatitis B virus, which is added to trigger a stronger immune response. The vaccine is designed to block the parasite's ability to infect the liver and mature there.

RTS,S was the first malaria vaccine to enter large trials in 2003. The initial results were encouraging, but hardly outstanding. The vaccine worked better when given to children starting at 6 months of age than in younger babies, which means it can't piggyback on the standard infant immunization schedule. And even then, the first three doses only cut the risk of clinical malaria by one-third. More concerning, there were hints the vaccine might increase the risk of developing cerebral malaria or catching meningitis. Another analysis of the data concluded overall mortality increased slightly in girls who received the vaccine.

Still, the data were promising enough for the European Medicines Agency to approve the vaccine for use in children ages 6 to 17 months old in July 2015. But a few months later, WHO's vaccine advisory panel decided the safety concerns and logistical hurdles needed more study and recommended a pilot rollout to better understand the vaccine's real-world impact. In response, WHO established the Malaria Vaccine Implementation Program, which began to administer the vaccine to children in selected regions in Ghana, Malawi, and Kenya in 2019.

Initial data from the first 2 years of the program showed the logistics hurdles could be surmounted: Between 62% and 67% of eligible children in the rollout regions received the first three doses. (The fourth dose is administered 12 to 18 months after the third dose, so most children have not yet received it.) The vaccine worked about as well as in earlier studies, lowering rates of hospitalization for severe malaria by about 30%. No increase in meningitis or overall mortality was observed. The data also showed vaccinations reached many of the most vulnerable children—those who don't sleep under bed nets. That shows how it can complement existing tools, says Abdoulaye Djimdé, a malaria expert at the University of Bamako in Mali.

During its meeting today, the panel also heard about data from a recent trial in which Djimdé and his colleagues used the vaccine in combination with regular doses of antimalarial drugs, given prophylactically just before the rainy season in Mali and Burkina Faso. Children who received both the vaccine and the antimalarials had a roughly 60% lower risk of clinical malaria and 70% lower risk of severe malaria compared with children who only received

one or the other. The combined data convinced the panel that a wider rollout was justified in areas of moderate to high malaria burden.

But several experts say regional patterns of malaria transmission should determine how the vaccine is used. For example, protection appears to be strongest in the first 6 months following vaccination, so in regions where malaria is concentrated in the rainy season, the vaccine is likely to be most helpful when it is given just before that season starts, similar to the way influenza vaccines are given in the fall.

Christine Stabell Benn, who studies vaccine impacts at the University of Southern Denmark, cautions that given the vaccine's waning protection, the data from the first 2 years of the pilot are "zooming in on the period of maximal benefit and minimal harm" from possible side effects, including rebound infections, in which children develop malaria after vaccine protection wears off.

Stabell Benn also notes that follow-up time in the pilot rollout was too short to measure whether the vaccine saved lives. The data showed a 7% decrease in mortality from any cause, but that was not statistically significant. "They set out to detect a 10% reduction in all-cause mortality. They haven't achieved that," she says. "And that's during the period it's supposed to be having the biggest effect."

The vaccine's cost could prove a drawback. GlaxoSmithKline, the company that makes RTS,S, has said it will sell doses at cost, plus a small markup that will go toward further research. The estimated $5 per dose is a bargain compared with many vaccines used in rich countries, but it still means countries will need to carefully consider how the vaccine fits in with other, less expensive malaria prevention tools, says Catherine Pitt, who studies the economics of malaria at the London School of Hygiene & Tropical Medicine. Although today's news is "fantastic," Pitt says, "the budget doesn't seem to be getting bigger, so hard choices have to be made."

WHO leaders said study of the best use of the vaccine will continue. "We'd all like a magic bullet," says Dyann Wirth, a malaria researcher at Harvard University and chair of WHO's Malaria Policy Advisory Group. "But this is a very complex disease that has evolved ways to evade the immune system," which makes vaccine development especially challenging. "We're not saying this is the end," Wirth says. "I'm hoping this is the beginning of a renaissance of vaccine development in the malaria field."

*doi: 10.1126/science.acx9310*

***https://bit.ly/3At3ro3***

## First drug for dengue, an excruciating disease, may be on the horizon

***"Breakbone fever" infects 400 million and kills 25,000 every year***

**By Dennis Normile**

Relief may be in sight for tropical hospitals that are increasingly overwhelmed during outbreaks of dengue, a viral disease that can cause excruciating pain and even death. A new study has identified a compound that blocks dengue virus replication in test tube experiments and in mice, and it might one day be available as an easy-to-take pill.

If it works in clinical trials in humans, the drug could be given at primary care clinics, "which would be very important for the developing world where dengue is hyperendemic," says Jenny Low, an infectious disease physician at Singapore General Hospital who was not involved in the work.

Dengue, which is spread by mosquitoes that thrive in urban areas, annually infects more than 400 million people, primarily in Asia and Latin America. Most cases are mild, and patients recover on their own. But an estimated 96 million people come down with bad fevers, rashes, and muscle and joint aches that can last about a week. The disease is caused by four related viruses, or serotypes;

subsequent infection with a different serotype increases the risk of internal bleeding and death. There are no drugs. During outbreaks, scores of patients with severe dengue rely on hospital care to manage the life-threatening symptoms.

The need to simultaneously protect against all four serotypes has stymied dengue vaccine development for decades. Finding a drug with balanced activity against all four was "like finding a needle in a haystack," says Johan Neyts, a virologist at KU Leuven who led the study.

Starting in 2009, Neyts's team screened tens of thousands of small molecules for antidengue activity using an automated high-throughput testing process. Chemists tweaked several molecules they found, producing more than 2000 compounds for further testing. One of those, named JNJ-A07, eventually proved equally potent against all four serotypes in test tube experiments. Next, the researchers administered the compound to mice, both before and after a dengue infection, to see whether the drug might be useful as a treatment, but also as a prophylactic. In both cases, the drug was "highly effective" in reducing viral loads and virus-induced disease, the team reports today in *Nature*.

The mouse results justify clinical trials for safety and efficacy in humans, says Cameron Simmons, an infectious disease scientist at Monash University, Clayton. But retired dengue researcher Scott Halstead, formerly of the Uniformed Services University of the Health Sciences, cautions against high expectations. "Experience has shown that the kind of in vitro data or even mouse model data cited here is not a reliable predictor of in vivo behavior," he says.

Further lab work suggested JNJ-A07 blocks the functioning of the replication complex, an assembly of five proteins that interact to enable the dengue virus to copy itself inside cells. By shedding light on how the dengue replication proteins interact, Neyts's work could lead to other drugs to treat the disease, says Eng Eong Ooi, a virologist at Duke-NUS Medical School in Singapore who was not involved in the study.

One apparent drawback is that for optimal effect, the drug would have to be given within a few days of symptom onset, before viral replication kicks into high gear. Many dengue patients don't seek medical help until the third or fourth day of illness. "The therapeutic window to provide clinical benefits is very brief," Simmons says.

"If you wait too long, it's too late," Neyts agrees. Deployment of the drug would need to be accompanied by educational campaigns for doctors and the public, he says. The drug could also be used as a prophylactic to blunt the impact of a community outbreak or by travelers visiting a dengue-endemic area, he says.

The drug is already in clinical trials, but Neyts declines to give details, saying scientists will present an update in November at the annual meeting of the American Society of Tropical Medicine & Hygiene. He also doesn't want to hazard a guess as to when a drug might become available.

For clinicians, Low says, that moment can't come soon enough: "The world has been searching for a direct-acting antiviral drug for decades." *doi: 10.1126/science.acx9305*

***https://bit.ly/3apkNrm***

## Natural Plant-Derived Compound Reduces Neurotoxicity in Alzheimer's Brain, Study Says

***Natural compound commonly present in plants such as basil decreases Alzheimer's disease pathology***

Fenchol, a natural compound commonly present in some plants including basil (*Ocimum basilicum*), decreases Alzheimer's disease pathology by activating the free fatty acid receptor 2 (FFAR2) signaling, according to new research published in the journal *Frontiers in Aging Neuroscience*.

Emerging evidence indicates that short-chain fatty acids (SCFAs)

— metabolites produced by beneficial gut bacteria and the primary source of nutrition for cells in your colon — contribute to brain health. The abundance of SCFAs is often reduced in older patients with mild cognitive impairment and Alzheimer's disease, the most common form of dementia.

However, how this decline in SCFAs contributes to Alzheimer's disease progression remains largely unknown. Gut-derived SCFAs that travel through the blood to the brain can bind to and activate FFAR2, a cell signaling molecule expressed on neurons.

"Our study is the first to discover that stimulation of the FFAR2 sensing mechanism by these microbial metabolites can be beneficial in protecting brain cells against toxic accumulation of the amyloid-beta (Aβ) protein associated with Alzheimer's disease," said Professor Hariom Yadav, a researcher at the Wake Forest School of Medicine and the University of South Florida.

In the study, Dr. Yadav and colleagues studied the function of FFAR2 in the brain. They first showed that inhibiting the FFAR2 receptor contributes to the abnormal buildup of the Aβ protein causing neurotoxicity linked to Alzheimer's disease.

Then, they performed large-scale virtual screening of more than 144,000 natural compounds to find potential candidates that could mimic the same beneficial effect of microbiota produced SCFAs in activating FFAR2 signaling.

"Identifying a natural compound alternative to SCFAs to optimally target the FFAR2 receptor on neurons is important, because cells in the gut and other organs consume most of these microbial metabolites before they reach the brain through blood circulation," Professor Yadav said.

The researchers narrowed 15 leading compound candidates to the most potent one. Fenchol was best at binding to the FFAR's active site to stimulate its signaling.

Further experiments in human neuronal cell cultures as well as Caenorhabditis elegans and mouse models of Alzheimer's disease demonstrated that fenchol significantly reduced excess Aβ accumulation and death of neurons by stimulating FFAR2 signaling, the microbiome sensing mechanism.

When the scientists more closely examined how fenchol modulates Aβ-induced neurotoxicity, they found that the compound decreased senescent neuronal cells, also known as 'zombie' cells, commonly found in brains with Alzheimer's disease pathology.

"Fenchol actually affects the two related mechanisms of senescence and proteolysis," Professor Yadav said. "It reduces the formation of half-dead zombie neuronal cells and also increases the degradation of (nonfunctioning) Aβ, so that amyloid protein is cleared from the brain much faster."

In exploring fenchol as a possible approach for treating or preventing Alzheimer's pathology, the team will seek answers to several questions.

"A key one is whether fenchol consumed in basil itself would be more or less bioactive (effective) than isolating and administering the compound in a pill," Professor Yadav said. "We also want to know whether a potent dose of either basil or fenchol would be a quicker way to get the compound into the brain."

*Atefeh Razazan et al. Activation of Microbiota Sensing – Free Fatty Acid Receptor 2 Signaling Ameliorates Amyloid-β Induced Neurotoxicity by Modulating Proteolysis-Senescence Axis. Front. Aging Neurosci, published online October 5, 2021; doi: 10.3389/fnagi.2021.735933*

***https://bit.ly/3AuDSD0***

## Muscle Regeneration: Massage Doesn't Just Feel Good, It Makes Muscles Heal Faster and Stronger

***Study in mice confirms link between mechanotherapy and immunotherapy in muscle regeneration.***

Massage has been used to treat sore, injured muscles for more than 3,000 years, and today many athletes swear by massage guns to rehabilitate their bodies. But other than making people feel good,

do these "mechanotherapies" actually improve healing after severe injury? According to a new study from researchers at Harvard's Wyss Institute for Biologically Inspired Engineering and John A. Paulson School of Engineering and Applied Sciences (SEAS), the answer is "yes."

Using a custom-designed robotic system to deliver consistent and tunable compressive forces to mice's leg muscles, the team found that this mechanical loading (ML) rapidly clears immune cells called neutrophils out of severely injured muscle tissue. This process also removed inflammatory cytokines released by neutrophils from the muscles, enhancing the process of muscle fiber regeneration. The research is published in *Science Translational Medicine*.

"Lots of people have been trying to study the beneficial effects of massage and other mechanotherapies on the body, but up to this point it hadn't been done in a systematic, reproducible way. Our work shows a very clear connection between mechanical stimulation and immune function. This has promise for regenerating a wide variety of tissues including bone, tendon, hair, and skin, and can also be used in patients with diseases that prevent the use of drug-based interventions," said first author Bo Ri Seo, Ph.D., who is a Postdoctoral Fellow in the lab of Core Faculty member Dave Mooney, Ph.D. at the Wyss Institute and SEAS.

**A more meticulous massage gun**

Seo and her coauthors started exploring the effects of mechanotherapy on injured tissues in mice several years ago, and found that it doubled the rate of muscle regeneration and reduced tissue scarring over the course of two weeks. Excited by the idea that mechanical stimulation alone can foster regeneration and enhance muscle function, the team decided to probe more deeply into exactly how that process worked in the body, and to figure out what parameters would maximize healing.

They teamed up with soft robotics experts in the Harvard Biodesign Lab, led by Wyss Associate Faculty member Conor Walsh, Ph.D., to create a small device that used sensors and actuators to monitor and control the force applied to the limb of a mouse. " The device we created allows us to precisely control parameters like the amount and frequency of force applied, enabling a much more systematic approach to understanding tissue healing than would be possible with a manual approach," said co-second author Christopher Payne, Ph.D., a former Postdoctoral Fellow at the Wyss Institute and the Harvard Biodesign Lab who is now a Robotics Engineer at Viam, Inc.

Once the device was ready, the team experimented with applying force to mice's leg muscles via a soft silicone tip and used ultrasound to get a look at what happened to the tissue in response. They observed that the muscles experienced a strain of between 10-40%, confirming that the tissues were experiencing mechanical force. They also used those ultrasound imaging data to develop and validate a computational model that could predict the amount of tissue strain under different loading forces.

They then applied consistent, repeated force to injured muscles for 14 days. While both treated and untreated muscles displayed a reduction in the amount of damaged muscle fibers, the reduction was more pronounced and the cross-sectional area of the fibers was larger in the treated muscle, indicating that treatment had led to greater repair and strength recovery. The greater the force applied during treatment, the stronger the injured muscles became, confirming that mechanotherapy improves muscle recovery after injury. But how?

**Evicting neutrophils to enhance regeneration**

To answer that question, the scientists performed a detailed biological assessment, analyzing a wide range of inflammation-related factors called cytokines and chemokines in untreated vs.

treated muscles. A subset of cytokines was dramatically lower in treated muscles after three days of mechanotherapy, and these cytokines are associated with the movement of immune cells called neutrophils, which play many roles in the inflammation process. Treated muscles also had fewer neutrophils in their tissue than untreated muscles, suggesting that the reduction in cytokines that attract them had caused the decrease in neutrophil infiltration.

The team had a hunch that the force applied to the muscle by the mechanotherapy effectively squeezed the neutrophils and cytokines out of the injured tissue. They confirmed this theory by injecting fluorescent molecules into the muscles and observing that the movement of the molecules was more significant with force application, supporting the idea that it helped to flush out the muscle tissue.

To pick apart what effect the neutrophils and their associated cytokines have on regenerating muscle fibers, the scientists performed *in vitro* studies in which they grew muscle progenitor cells (MPCs) in a medium in which neutrophils had previously been grown. They found that the number of MPCs increased, but the rate at which they differentiated (developed into other cell types) decreased, suggesting that neutrophil-secreted factors stimulate the growth of muscle cells, but the prolonged presence of those factors impairs the production of new muscle fibers.

“Neutrophils are known to kill and clear out pathogens and damaged tissue, but in this study we identified their direct impacts on muscle progenitor cell behaviors,” said co-second author Stephanie McNamara, a former Post-Graduate Fellow at the Wyss Institute who is now an M.D.-Ph.D. student at Harvard Medical School (HMS). “While the inflammatory response is important for regeneration in the initial stages of healing, it is equally important that inflammation is quickly resolved to enable the regenerative processes to run its full course.”

Seo and her colleagues then turned back to their *in vivo* model and analyzed the types of muscle fibers in the treated vs. untreated mice 14 days after injury. They found that type IIX fibers were prevalent in healthy muscle and treated muscle, but untreated injured muscle contained smaller numbers of type IIX fibers and increased numbers of type IIA fibers. This difference explained the enlarged fiber size and greater force production of treated muscles, as IIX fibers produce more force than IIA fibers.

Finally, the team homed in on the optimal amount of time for neutrophil presence in injured muscle by depleting neutrophils in the mice on the third day after injury. The treated mice’s muscles showed larger fiber size and greater strength recovery than those in untreated mice, confirming that while neutrophils are necessary in the earliest stages of injury recovery, getting them out of the injury site early leads to improved muscle regeneration.

“These findings are remarkable because they indicate that we can influence the function of the body’s immune system in a drug-free, non-invasive way,” said Walsh, who is also the Paul A. Maeder Professor of Engineering and Applied Science at SEAS and whose group is experienced in developing wearable technology for diagnosing and treating disease. “This provides great motivation for the development of external, mechanical interventions to help accelerate and improve muscle and tissue healing that have the potential to be rapidly translated to the clinic.”

The team is continuing to investigate this line of research with multiple projects in the lab. They plan to validate this mechanotherpeutic approach in larger animals, with the goal of being able to test its efficacy on humans. They also hope to test it on different types of injuries, age-related muscle loss, and muscle performance enhancement.

“The fields of mechanotherapy and immunotherapy rarely interact with each other, but this work is a testament to how crucial it is to

consider both physical and biological elements when studying and working to improve human health," said Mooney, who is the corresponding author of the paper and the Robert P. Pinkas Family Professor of Bioengineering at SEAS.

"The idea that mechanics influence cell and tissue function was ridiculed until the last few decades, and while scientists have made great strides in establishing acceptance of this fact, we still know very little about how that process actually works at the organ level. This research has revealed a previously unknown type of interplay between mechanobiology and immunology that is critical for muscle tissue healing, in addition to describing a new form of mechanotherapy that potentially could be as potent as chemical or gene therapies, but much simpler and less invasive," said Wyss Founding Director Don Ingber, M.D., Ph.D., who is also the *Judah Folkman Professor of Vascular Biology* at (HMS) and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at SEAS.

*Reference: "Skeletal muscle regeneration with robotic actuation-mediated clearance of neutrophils" 6 October 2021, Science Translational Medicine.*

*Additional authors of the paper include Benjamin Freedman, Brian Kwee, Sungmin Nam, Irene de Lázaro, Max Darnell, Jonathan Alvarez, and Maxence Dellacherie from the Wyss Institute and SEAS, and Herman H. Vandenburgh from Brown University.*

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***https://bit.ly/2YJwyqi***

## The most common Alzheimer's risk gene may also protect against memory loss

***APOE4's ability to blunt cognitive decline may help explain why it persists***

**By Jocelyn Kaiser**

A common genetic variant called *APOE4* raises a person's risk of Alzheimer's disease. It also poses a puzzle: If *APOE4* is so bad for us, why hasn't it been weeded out from the population? A new study finds that, surprisingly, the *APOE4* variant has positive cognitive impacts: It may not only boost short-term memory, but also protect against subtle memory loss early in the course of Alzheimer's disease.

"There is something about the possession of an *APOE4* allele which is providing some positive impacts on your cognitive function," even in people whose brains are primed for Alzheimer's, says neurologist Jonathan Schott of University College London (UCL), co-leader of the study. That could not only help explain why the variant persists, but also guide Alzheimer's treatments, he says.

The *APOE* gene codes for a protein called apolipoprotein E, which helps metabolize fats. About one in four people carry one copy of the version called *APOE4* that roughly triples the risk for late-onset Alzheimer's disease. (A few people have two copies of *APOE4*, which raises the risk 12-fold or more.)

When a harmful gene remains in a population across hundreds of thousands of years, one possible explanation for its staying power is that one copy is beneficial. For example, people with one copy of the sickle cell gene are protected from malaria.

Scientists have known for years that people with *APOE4* are more likely to develop sticky amyloid protein plaques in their brains; many researchers think these may contribute to Alzheimer's by triggering other changes that lead to neuronal death. Yet several small studies have hinted that *APOE4* could have benefits, such as boosting fertility and cognition. Last year, a larger study found that *APOE4* carriers across a range of ages perform slightly better than noncarriers on a test requiring them to quickly recall an object and its location.

In the new work, researchers at UCL studied 398 people around age

70 who had been followed by researchers since birth. The participants all had normal results on standard cognitive tests, and none had been diagnosed with Alzheimer's. Unlike the previous study, the researchers also conducted brain scans and found that some had signs of amyloid plaques.

To test for subtle cognitive deficits, researchers had the volunteers sit in front of a computer screen on which a single object with a fractal pattern briefly appeared. After a few seconds, two objects—one new—popped up, and the person had to identify the one they had seen before and slide it to its original location.

Those with *APOE4* were 14% better at identifying the object and 7% better at relocating it than participants without the mutation. And in people with amyloid buildup—who overall fared 19% worse on the identification task—*APOE4* seemed to have a beneficial effect, particularly in the relocation test for people with higher amyloid levels, Schott and colleagues report today in *Nature Aging*. "These are small and subtle changes, but suggest that amyloid and *APOE4* have opposite effects on visual short-term memory," Schott says.

The benefits of *APOE4* are limited, however. Carriers also performed better on some verbal tests of short-term memory, but not on long-term memory tests. And as amyloid accumulates, the resulting cognitive deficits will likely swamp out any boost from *APOE4*, the authors say.

"It is striking that the cognitive advantage [from *APOE4*] is observed even in the presence of Alzheimer's pathology," says neuropsychologist Duke Han of the University of Southern California, who was not involved in the work.

Still unclear is exactly how this would help *APOE4* persist across generations. The cognitive boost conferred by *APOE4* in younger people could be enough to explain its continued presence in the gene pool. For example, the boost it gives to short-term memory could have been a strong advantage when our hunter-gatherer ancestors were out looking for food.

University of Oxford psychologist Nahid Zokaei, lead author on the 2020 paper on *APOE4* and short-term memory, says the findings could shed light on "the mechanism of Alzheimer's and how our brain works" by revealing "how these compensatory mechanisms kick in and take up the slack."

The study should also give pause to researchers developing Alzheimer's treatments that block *APOE4*'s protein, Schott says. "If we're thinking about targeting *APOE4*, we really need to know what the advantages and the disadvantages might be at different ages."

*doi: 10.1126/science.acx9319*

***https://bit.ly/3mKYzGi***

## Curing with blood: the rise and fall of COVID convalescent plasma therapy

***Early in the pandemic, scientists thought "convalescent plasma" might be a way to treat COVID-19.***

**Andrew McLachlan***
**Sophie Stocker****

By giving patients the plasma of people who had recovered (or convalesced) from COVID-19, the idea was this antibody-rich infusion would help their immune systems fight infection. It's a strategy tried, with various degrees of success, for other infectious diseases, including Ebola.

But growing evidence, including an international study published this week, shows convalescent plasma does not save lives of people critically ill with COVID-19. The researchers concluded the therapy was "futile".

**What is convalescent plasma?**

Convalescent plasma is a blood product containing antibodies against an infectious pathogen (such as SARS-CoV-2, the coronavirus that causes COVID-19). It comes from blood collected

from people who have recovered from the infectious disease.

Scientists use a process called apheresis to separate the different blood components. Red and white cells, and platelets are removed leaving plasma, which is rich in antibodies.

The story of convalescent plasma therapy (or serum therapy) originates in the 1890s. This is when physician Emil von Behring infected horses with the bacteria that causes diphtheria.

Once the horses recovered, Behring collected their antibody-rich blood to treat humans with the disease. This led to him being awarded the first Nobel prize in physiology or medicine, in 1901.

**Why has convalescent plasma been used to treat COVID?**

Convalescent plasma has been used to treat infectious diseases for over a century. These include: scarlet fever, pneumonia, tetanus, diphtheria, mumps and chickenpox.

More recently, convalescent plasma has been investigated as a treatment for SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome) and Ebola. So early in the pandemic, researchers hoped convalescent plasma could be used to treat COVID-19 too. Initial studies and some clinical trials were promising. This led to the widespread use of convalescent plasma for patients with COVID-19 in the United States, a decision supported by the Food and Drug Administration.

By May this year more than 100 clinical trials had been conducted with convalescent plasma in people with COVID-19; about one-third of these studies had finished or were stopped early.

Earlier this year, the results of the United Kingdom's landmark RECOVERY trial were reported. This investigated convalescent plasma therapy (compared to usual supportive care) in more than 10,000 people hospitalised with COVID-19.

Treatment did not reduce the risk of death (24% in both groups), with no difference in the number of patients who recovered (66% discharged from hospital in both groups) or who got worse (29% needed mechanical ventilation to support breathing in both groups).

So for people admitted to hospital with COVID-19, the researchers concluded convalescent plasma offered no benefit.

A Cochrane review, which was updated in May this year and evaluated all available trials, confirmed these results. These trials involved more than 40,000 people with moderate-to-severe COVID-19 who received convalescent plasma.

The review found the treatment had no effect on the risk of dying from COVID-19, did not reduce the risk of requiring hospitalisation nor the need for a ventilator to assist breathing when compared to placebo or standard care. In Australia, the National COVID-19 Clinical Evidence Taskforce does not recommend using convalescent plasma in people with COVID-19, unless it is in a clinical trial.

**What's the latest news?**

The results of the trial reported this week come from a major clinical trial involving about 2,000 hospitalised patients with moderate-to-severe COVID-19. Patients were randomised to receive convalescent plasma or usual care. All patients had access to other supportive medicines used in critically ill hospitalised people with COVID, such as dexamethasone and remdesivir.

The international team of investigators included those from Australia, Canada, UK and US.

Although the results and detailed analysis were published this week, the trial was halted in January. This is when the trial committee reviewed the interim results and reported "convalescent plasma was unlikely to be of benefit for patients with COVID-19 who require organ support in an intensive care unit". So continuing the trial was considered futile.

Convalescent plasma treatment did not reduce the risk of death in hospital over the month after treatment (37.3% convalescent plasma treated, 38.4% usual care, not treated with convalescent plasma).

The median number of days without the need for organ support (such as a mechanical ventilator or cardiac support) was 14 days in both groups. Serious adverse events were reported in 3.0% of people treated with convalescent plasma and only 1.3% in the usual care group. Taken together, the weight of evidence now clearly demonstrates convalescent plasma is not a treatment option for people with mild, moderate or even severe COVID-19.

**Where next for COVID-19 treatments?**

While vaccinations remain the major strategy to prevent COVID-19, attention is now turning to some emerging and promising treatments to prevent COVID-19 worsening.

These include emerging antiviral treatments that may be used early in the disease, including monoclonal antibodies such as sotrovimab and AZD7442. Then there are potential oral antiviral medicines, such as molnupiravir and PF-07321332.

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**Senior Lecturer, Sydney Pharmacy School, University of Sydney

***Disclosure statement*** *Andrew McLachlan receives research funding from the NHMRC and the Sydney Pharmacy School receives research scholarship funding from GSK for a PhD student under his supervision. Andrew has served as a paid consultant on Australian government committees related to medicines regulation. Andrew does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article.*

*Sophie Stocker receives funding from foundations which support medical research including Arthritis Australia, Heart Foundation and St Vincent's Clinic Foundation.*

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***https://bit.ly/3avsVGJ***

## Global plan aims to slash meningitis toll with help of new five-in-one vaccine

### *WHO "road map" would end epidemics in Africa and cut deaths worldwide by 70%*

**By Leslie Roberts**

When the sudden, terrifying deaths hit in early June in Banalia, a small mining community in northeastern Democratic Republic of the Congo (DRC), some people suspected witchcraft. Many of the victims were young men living in overcrowded barracks who had come to mine gold and other riches, and rather than seek treatment, they fled, carrying the mysterious ailment with them.

Health authorities were slow to recognize the cause. Banalia is in Tshopo province, which sits in the African meningitis belt, a band stretching from Ethiopia in the east to Senegal in the west, but the province had not seen meningitis outbreaks since 2009. And the puzzling affliction occurred outside the normal meningitis season, which starts in December, when the fierce Harmattan winds whip up the desert dust across large parts of the belt, and ends when the rains begin in June. This year, however, the rains were late.

The DRC suspected meningitis by July and started to provide antibiotic treatment in August, but it wasn't until 7 September that the Pasteur Institute in Paris identified a familiar cause of meningitis, a bacterium named *Neisseria meningitides* serotype W. The country declared an outbreak and applied for vaccines from an international stockpile, but by then the disease had spread around Tshopo province. As of 3 October, 1349 suspected cases and 189 deaths had been reported. Initially, the fatality rate was a shocking 84%; "Many people didn't arrive at health centers until they were in coma," says André Bita Fouda, meningitis lead for the World Health Organization (WHO) Africa region.

A new "global road map," launched by WHO and many partners on 28 September, could help prevent such tragedies in the future. With the help of a new vaccine targeting five serotypes of *N. meningitidis*, including W, it aims to eliminate epidemics of bacterial meningitis, which kill an estimated 250,000 a year in Africa, by 2030. It would also step up the fight against sporadic cases and small clusters of the disease that occur around the world. Cases worldwide—now some 5 million per year—would be halved by 2030 and deaths reduced by 70%.

The road map, which does not yet have a price tag, is "very ambitious," says WHO's Marie-Pierre Préziosi, who led its development, "but I do think it is feasible"—provided extra money comes through. Still, "How many road maps have been launched before but lost their way?" Mike Ryan, head of health emergencies at WHO, cautioned at the plan's launch. "We must see we don't lose our way on this one."

Meningitis, an inflammation of the membranes shielding the brain and spinal cord, can also be caused by viruses and fungi. But only bacteria spawn the epidemics that sweep across the meningitis belt every 5 to 12 years. Spread by respiratory droplets, bacterial meningitis kills one in 10 affected, often within 24 hours, and leaves one in five with lifelong disabilities such as deafness, cognitive impairment, and loss of limbs. Some people "carry" the bacteria in their nose and throat harmlessly. Trouble strikes, the leading theory goes, when dust and dry weather aggravate the mucous membranes, giving the bacteria a route to invade the bloodstream.

Vaccines already exist for three of the four bacterial species, but they don't cover all serotypes. Many were developed for high-income countries; their price puts them out of reach in Africa, and some are in short supply. That's why the Geneva-based International Coordinating Group on Vaccine Provision (ICG) doles them out only after an outbreak has begun, which is little more than a "Band-Aid," says Mark Alderson, who heads the bacterial meningitis vaccine effort at PATH in Seattle.

The hugely successful 2010 introduction of a long-lasting vaccine against *N. meningitides* group A, which at the time caused 80% to 90% of all epidemics in Africa, shows the promise of vaccines. Developed by a collaboration between PATH and the Serum Institute of India, it consists of a polysaccharide from the bacterium's surface linked to a protein, tetanus toxoid, that makes the vaccine more powerful. The final price tag was a mere 60 cents per dose, making it cheap enough to use in mass vaccination campaigns.

So far, 24 of the 26 countries in the meningitis belt have introduced the vaccine, MenAfriVac, in mass campaigns; 11 have also incorporated it into routine child hood immunization. The impact has been stunning: The last outbreak of meningitis A occurred in 2014, and the last known case in 2017. (Other *N. meningitidis* serotypes and *Streptococcus* partially replaced the strain, however.)

Now, PATH and Serum are trying to duplicate that success with a "pentavalent" conjugate vaccine that protects against *N. meningitidis* serotypes A, C, Y, W, and X. "If we can switch from MenAfriVac to pentavalent, it could be the end of epidemics in Africa," Préziosi says.

It's a tall order, essentially five vaccines in one. Results from phase 3 clinical trials conducted in Mali and Gambia are not public yet but look encouraging, Alderson says. The partners expect the vaccine to be licensed and receive WHO prequalification—the official blessing for use in poor countries—in 2022. "There is a real sense of urgency coming from WHO," Alderson says.

The price, up to $3 a dose, could still pose a problem. WHO and Gavi, the Vaccine Alliance, which funds vaccines for poor countries, are discussing ways to keep the cost down. MenAfriVac is given to 1- to 29-year-olds, who are most vulnerable to bacterial meningitis; one possibility is to lower the upper age limit for the pentavalent vaccine. Another option is to use it both in mass vaccination campaigns and routine immunization in high-burden countries, but drop the mass campaigns where epidemics occur less often.

The road map also aims for wider use of existing meningitis vaccines and the development of affordable new ones, including against group B *Streptococcus*. The only one of the four species for

which no vaccines exist, it is a leading cause of newborn meningitis worldwide.

Meeting WHO's targets will also require stepped up surveillance and affordable, rapid tests so that infected people can be identified and treated with antibiotics. (Now, diagnosis requires a lumbar puncture, which health workers in poor countries don't always perform.) People living with the disease's long-term consequences also need better care and rehabilitation.

In the DRC, weekly case numbers are still climbing, Bita Fouda says. But antibiotics have lowered the death rate to about 10%, and a team of neurologists is helping diagnose and treat complications. ICG approved the DRC's request for 187,460 vaccine doses on 17 September, and the shots arrived in the country on 2 October. Once vaccinations begin, Bita Fouda says, "we should see a drop in cases in 4 to 6 weeks." *doi: 10.1126/science.acx9300*

***https://bit.ly/3lnOUWt***

## Extinct Ground Sloth – Mylodon darwinii – Likely Ate Meat With Its Veggies

***New study reveals that Mylodon was an omnivore, unlike its strictly plant-eating relatives.***

A new study led by researchers at the American Museum of Natural History suggests that *Mylodon*—a ground sloth that lived in South America until about 10,000 to 12,000 years ago—was not a strict vegetarian like all of its living relatives. Based on a chemical analysis of amino acids (fundamental biological compounds that are the building blocks of proteins) preserved in sloth hair, the researchers uncovered evidence that this gigantic extinct sloth was an omnivore, at times eating meat or other animal protein in addition to plant matter. The study, published today (October 7, 2021) in the journal *Scientific Reports*, contradicts previous assumptions in the field.

"Whether they were sporadic scavengers or opportunistic consumers of animal protein can't be determined from our research, but we now have strong evidence contradicting the long-standing presumption that all sloths were obligate herbivores," said lead author Julia Tejada, a Museum research associate and postdoctoral researcher at the University of Montpellier, France. Tejada began the work on this study as a Ph.D. student in the Museum's Richard Gilder Graduate School collaborative program with Columbia University.

Even though the six living sloth species all are relatively small plant-eating tree-dwellers restricted to tropical forests of Central and South America, hundreds of fossil sloth species, some as large as an elephant, roamed ancient landscapes from Alaska to the southern tip of South America. *Mylodon darwinii*, also known as "Darwin's ground sloth," is thought to have weighed between 2,200 and 4,400 pounds and was nearly 10 feet long. Based on dental characteristics, jaw biomechanics, preserved excrement from some very recent fossil species, and the fact that all living sloths exclusively eat plants, *Mylodon* and its extinct relatives have long been presumed to be herbivores as well. But these factors could not directly reveal whether an animal might have ingested food that requires little or no preparation and is completely digested, as happens in carcass scavenging or some other kinds of meat-eating.

To get a more complete picture, the new study uses an innovative approach based on nitrogen isotopes locked into specific amino acids within animal body parts, known as "amino acid compound-specific isotope analysis." Found in different proportions in the food consumed by an animal, stable nitrogen isotopes are also preserved in their body tissues—including hair and other keratinous tissues like fingernails, as well as in collagen like that found in teeth or bones. By first analyzing the amino-acid nitrogen values in a wide range of modern herbivores and omnivores to determine a clear signal of eating a mix of plant and animal food, fossils can

then be measured to determine the food they consumed. This offers paleontologists a unique window directly into the diets of animals, enabling them to determine their "trophic level"—whether they were plant-eating herbivores, mixed-feeding omnivores, meat-eating carnivores, or specialized marine animal consumers.

"Prior methods relied solely on bulk analyses of nitrogen and complex formulas that have many untested or weakly supported assumptions. Our analytical approach and results show that many previous conclusions about tropic levels are poorly supported at best, or clearly wrong and misleading at worst," said study co-author John Flynn, Frick Curator of Fossil Mammals in the Museum's Division of Paleontology.

The researchers used samples from seven living and extinct species of sloths and anteaters (which are closely related to sloths), as well as from a wide range of modern omnivores, from the scientific collections of the Museum's Mammalogy and Paleontology Departments and from the Yale Peabody Museum. While the other extinct sloth in the study, the North American ground sloth *Nothrotheriops shastensis*, was determined to be an exclusive herbivore, the data clearly flagged *Mylodon* as an omnivore.

Prior research speculated that there were more herbivores than could be supported by the available plants in ancient ecosystems of South America, suggesting that some of those herbivores may have been finding other sources of food. This new study provides compelling evidence supporting that previously untested idea.

"These results, providing the first direct evidence of omnivory in an ancient sloth species, demands reevaluation of the entire ecological structure of ancient mammalian communities in South America, as sloths represented a major component of these ecosystems across the past 34 million years," Tejada said.

*Reference: "Isotope data from amino acids indicate Darwin's ground sloth was not an herbivore" by Julia V. Tejada, John J. Flynn, Ross MacPhee, Tamsin C. O'Connell, Thure E. Cerling, Lizette Bermudez, Carmen Capuñay, Natalie Wallsgrove and Brian N. Popp, 7 October 2021, Scientific Reports.*
*DOI: 10.1038/s41598-021-97996-9*

*Other authors on this study include Ross MacPhee, from the American Museum of Natural History; Tamsin O'Connell from the University of Cambridge; Thure Cerling from the University of Utah; Lizette Bermudez and Carmen Capuñay from the Huachipa Zoo in Lima, Peru; and Natalie Wallsgrove and Brian Popp from the University of Hawai'i at Manoa.*

*This work was funded by The Frick Fund (Vertebrate Paleontology, American Museum of Natural History), the Lamont Doherty Earth Observatory's Chevron Student Initiative Fund, the Paleontological Society, and the School of Ocean and Earth Sciences of the University of Hawai'i at Manoa.*

***https://wb.md/3uX16kj***

## Constipation Med Boosts Cognitive Performance in Mental Illness

***A drug approved to treat constipation appears to improve cognitive impairment and boost brain activity for patients with mental illness, new research suggests.***

**Liam Davenport**

In a randomized controlled trial, 44 healthy individuals were assigned to receive the selective serotonin-4 (5-HT4) receptor agonist prucalopride (Motegrity) or placebo for 1 week.

After 6 days, the active-treatment group performed significantly better on memory tests than the participants who received placebo. In addition, the drug increased activity in brain areas related to cognition.

"What we're hoping is...these agents may be able to help those with cognitive impairment as part of their mental illness," lead author Angharad N. de Cates, a clinical DPhil student in the Department of Psychiatry, University of Oxford, Oxford, United Kingdom, told meeting attendees. "Currently, we're looking to see if we can translate our finding a step further and do a similar study in those with depression," de Cates added.

The findings were presented at the 34th European College of Neuropsychopharmacology (ECNP) Congress and were

simultaneously published in *Translational Psychiatry.*

**"Exciting Early Evidence"**

"Even when the low mood associated with depression is well-treated with conventional antidepressants, many patients continue to experience problems with their memory," co-investigator Susannah Murphy, PhD, a senior research fellow at the University of Oxford, said in a release. "Our study provides exciting early evidence in humans of a new approach that might be a helpful way to treat these residual cognitive symptoms," Murphy added.

Preclinical and animal studies suggest that the 5-HT4 receptor is a promising treatment target for cognitive impairment in individuals with psychiatric disorders, although studies in humans have been limited by the adverse effects of early agents.

"We've had our eye on this receptor for a while," explained de Cates, inasmuch as the animal data "have been so good."

However, she told *Medscape Medical News* that "a lack of safe human agents made translation tricky."

As previously reported, prucalopride, a selective high-affinity 5-HT4 partial agonist, was approved in 2018 by the US Food and Drug Administration for the treatment of chronic idiopathic constipation.

The current researchers note that the drug has "good brain penetration," which "allowed us to investigate 5-HT4-receptor agonism in humans."

Having previously shown that a single dose of the drug has "pro-cognitive effects," the investigators conducted the new trial in 44 healthy participants. All were randomly assigned in a 1:1 ratio to receive either prucalopride 1 mg for 7 days or placebo.

In accordance with enrollment criteria, patients were 18 to 36 years of age, right-handed, and were not pregnant or breastfeeding. Participants' body mass index was 18 to 30 kg/m$^2$, and they had no contraindications to the study drug. The two treatment groups were well balanced; the participants who received placebo were significantly more likely to be nonnative English speakers ($P$ = .02).

On day 6 of treatment administration, all participants underwent 3T MRI.

Before undergoing imaging, the participants were presented with eight emotionally neutral images of animals or landscapes and were asked to indicate whether or not the images were of animals. The task was then repeated with the eight familiar images and eight novel ones.

During the scan, participants were shown the same images or eight novel images and were again asked whether or not the images contained an animal. They were also instructed to try to remember the images for a subsequent memory task. In that task, the eight original images, 48 novel images, and 27 "distractor" images were presented.

**Better Memory**

In the pre-scan assessment, results showed no significant differences in the ability of members of the prucalopride and placebo groups to identify images as being familiar or different.

However, taking prucalopride was associated with significantly improved memory performance in the post-scan recall task.

Compared to the placebo group, participants in the prucalopride group were more accurate in selecting images as familiar vs distractors ($P$ = .029) and in distinguishing images as familiar, novel, or distractors ($P$ = .035).

Functional MRI revealed increased activity in the left and right hippocampus in response to both novel and familiar images among the participants in the prucalopride group in comparison with those in the placebo group. There was also increased activity in the right angular gyrus in the prucalopride group in comparison with the placebo group in response to familiar images ($P$ < .005).

"Clinically, angular gyri lesions cause language dysfunction, low

mood, and poor memory and can mimic dementia or pseudodementia," the investigators write. They note that the right angular gyrus "shows significantly decreased activity" in mild cognitive impairment.

"Therefore, the increased activity seen in the right angular gyrus following prucalopride administration in our study is consistent with the pro-cognitive behavioural effects we observed," they add.

De Cates noted that the dose used in their study was lower than the 2 mg given for constipation.

"At the low dose, there were no differences in side effects between groups and no withdrawals from the prucalopride group for side effects. We are going to try increasing the dose in our next study actually, as we don't have PET [positron-emission tomography] data to tell us what the optimal dose for binding at the receptor should be," said de Cates. "In safety studies, the dose was trialled in healthy volunteers at 4mg, which was found to be safe, although perhaps less well tolerated than 2 mg," she said.

**Generalizable Findings?**

Commenting on the research, Vibe G. Frøkjær, MD, adjunct professor, Department of Psychology, Copenhagen University, Copenhagen, Denmark, said the study "highlights a very interesting and much needed potential for repurposing drugs to help cognitive dysfunction." He noted that cognitive dysfunction is often associated with psychiatric disorders — even in states of remission.

"Importantly, as the authors also state, it will be vital to translate these findings from healthy populations into clinical populations," said Frøkjær, who was not involved in the research.

"It will also be important to understand if prucalopride adds to the effects of existing antidepressant treatments or can be used as a stand-alone therapy," he added.

*The study was funded by the NIHR Oxford Health Biomedical Research Center and by the Wellcome Center for Integrative Neuroscience. De Cates has received a travel grant from the Royal College of Psychiatrists/Gatsby Foundation and support from Wellcome. The other authors have relationships with P1vital Ltd, Janssen Pharmaceuticals, Sage Therapeutics, Pfizer, Zogenix, Compass Pathways, and Lundbeck.*

*34th European College of Neuropsychopharmacology (ECNP) Congress: Abstract IN.08.03. Presented October 4, 2021.*

*Transl Psychiatry. Published online October 4, 2021. Full text*

***https://bit.ly/3oRdOA6***

# Study traces the evolution of the hepatitis B virus from prehistory to the present

## *Analyzing the largest dataset of ancient viral genomes produced to date*

In a new paper in the journal *Science*, researchers uncover the evolution of the hepatitis B virus since the Early Holocene by analyzing the largest dataset of ancient viral genomes produced to date.

The hepatitis B virus (HBV) is a major health problem worldwide, causing close to one million deaths each year. Recent ancient DNA studies have shown that HBV has been infecting humans for millennia, but its past diversity and dispersal routes remain largely unknown. A new study conducted by a large team of researchers from all around the world provides major insights into the evolutionary history of HBV by examining the virus' genomes from 137 ancient Eurasians and Native Americans dated to between ~10,500 and ~400 years ago. Their results highlight dissemination routes and shifts in viral diversity that mirror well-known human migrations and demographic events, as well as unexpected patterns and connections to the present.

**HBV and the peopling of the Americas**

Present-day HBV strains are classified into nine genotypes, two of which are found predominantly in populations of Native American ancestry. The study provides strong evidence that these strains descend from an HBV lineage that diverged around the end of the Pleistocene and was carried by some of the first inhabitants of the Americas.

"Our data suggest that all known HBV genotypes descend from a strain that was infecting the ancestors of the First Americans and their closest Eurasian relatives around the time these populations diverged," says Denise Kühnert, leader of the tide research group and supervisor of the study.

**HBV in prehistoric Europe**

The study also shows that the virus was present in large parts of Europe as early as 10,000 years ago, before the spread of agriculture to the continent.

"Many human pathogens are thought to have emerged after the introduction of agriculture, but HBV was clearly already affecting prehistoric hunter-gatherer populations," says Johannes Krause, director of the Department of Archaeogenetics at the Max Planck Institute for Evolutionary Anthropology and co-supervisor of the study.

After the Neolithic transition in Europe, the HBV strains carried by hunter-gatherers were replaced by new strains that were likely spread by the continent's first farmers, mirroring the large genetic influx associated with the expansion of farming groups across the region. These new viral lineages continued to prevail throughout western Eurasia for close to 4,000 years. The dominance of these strains lasted through the expansion of Western Steppe Herders around 5,000 years ago, which dramatically altered the genetic profile of Europeans but remarkably was not associated with the spread of new HBV variants.

**The collapse and re-emergence of pre-historic HBV**

One of the most surprising findings of the study is a sudden decline of HBV diversity in western Eurasia during the second half of the 2nd millennium BCE, a time of major cultural shifts, including the collapse of large Bronze Age state societies in the eastern Mediterranean region.

"This could point to important changes in epidemiological dynamics over a very large region during this period, but we will need more research to understand what happened," says Arthur Kocher, lead author and researcher in the tide group.

All ancient HBV strains recovered in western Eurasia after this period belonged to new viral lineages that still prevail in the region today. However, it appears that one variant related to the previous pre-historic diversity of the region has persisted to the present. This prehistoric variant has evolved into a rare genotype that seems to have emerged recently during the HIV pandemic, for reasons that remain to be understood.

***More information:*** *Arthur Kocher et al, Ten millennia of hepatitis B virus evolution, Science (2021).* *DOI: 10.1126/science.abi5658*

***https://wb.md/3lvpsOS***

## Shout It From the Rooftops: Undetectable = Untransmittable!

### *U=U, tell everybody!*

**Jemma Alarcón, MD, MPH**

They are walking at night, Dontae is wearing a black leather jacket and Troy a brown one. Their path in the park is well lit, surrounded by trees. They are about to kiss, but Dontae stops him, Troy asks, "What's the matter?" Dontae responds, "There is something we should talk about." The mood becomes tense.

Dontae seems nervous, eyes tearful, "I am undetectable…HIV positive."

Troy becomes upset. Dontae pleads, "I never put you at risk, we used a condom — I am undetectable." Troy repeats, "You should have told me. You took away my choice." Dontae responds. "I took my meds. By taking my meds, I made sure that you couldn't catch it." Troy, visibly upset, walks away from Dontae leaving him alone.

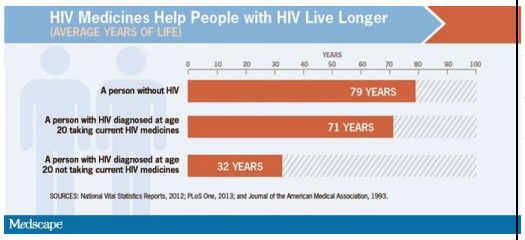
Alone — how many folks living with HIV still feel.

Designated Survivor, a Netflix show that unfortunately was cancelled (I would watch a fourth season, for what is worth),

introduced the audience to what must be a very common situation: the HIV-positive partner, in this case a man, sharing his status with his partner. A few episodes later, Dontae tells Troy that he acted like a bigot because U=U (undetectable = untransmittable).

Although disclosing your status, especially when it has to do with sexually transmitted infections, to a partner you hope to be intimate with is the right thing to do (ideally before any sexual encounter) Dontae is right that U=U. If you are living with HIV and taking your HIV medication every day, if your viral load is undetectable (meaning that a PCR test cannot replicate any virus because too little is to be found in your blood), you cannot transmit HIV.

In the 40 years since HIV/AIDS was first discovered, we have come a long way. The life expectancy of folks living with HIV is now comparable to the general population.

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As a family medicine resident, I have the opportunity to care for folks with HIV. I tell my patients that our advances in treating it are so great that your family doctor can treat it, just like we treat hypertension and diabetes.

Despite this, the stigma is well and alive — Silence = Death continues to be fitting. New HIV cases are diagnosed every day, and many will not know until they have AIDS.

A classic teaching is that some individuals with new HIV will experience flulike illness soon after transmission. Patients with AIDS (defined as a CD4 cell count < 200 and/or presenting with an AIDS-defining condition) will often present with significant weight loss, decreased appetite, and diarrhea.

Many still see HIV as a life sentence and will suffer from depression and often not tell anyone, even their therapist, that they have it.

We, as a society, have to step up. If the viral load is null, not enough virus around to be detected, then the person will not be able to transmit the virus.

Dontae was probably afraid of being stigmatized and with good reason. Until we all see it as the preventable, treatable, untransmittable disease, silence will continue to equal death.

In a later episode, Troy shares with Dontae that his doctor agreed that U=U and apologized for his strong reaction. Physicians have the opportunity to help their patients understand this concept as well.

Even if you are not treating their HIV, you can remind them that if their viral load is undetectable, they are unlikely to transmit the virus and can lead longer, healthier lives. You can also ask what their understanding of the disease is and share the good news.

For more information, the National Institute of Health looks at the science evidence of U=U.

*PS: Here is a link on how to become HIV certified as a family doc: https://aahivm.org/credentialing/*

***https://bit.ly/3DsSPYf***

## New Vaccination Strategy Developed That Could Prevent Future Coronavirus Outbreaks

***Vaccination strategy in mice promotes the production of antibodies that can neutralize not only SARS-CoV-2 but a broad range of other coronaviruses***

Researchers in Japan have developed a vaccination strategy in mice that promotes the production of antibodies that can neutralize not only SARS-CoV-2 but a broad range of other coronaviruses as well. If successfully translated to humans, the approach, to be published today (October 8, 2021), in the *Journal of Experimental Medicine*, could lead to the development of a next-generation vaccine capable of preventing future coronavirus pandemics.

The SARS-CoV-2 virus responsible for COVID-19 enters human cells by using its spike protein to bind to a cell surface receptor called ACE2. The receptor-binding domain of the spike protein consists of two parts: a "core" region that is very similar in all coronaviruses, and a more specialized "head" region that mediates binding to ACE2.

Antibodies that recognize the head region of the spike receptor-binding domain can block the entry of SARS-CoV-2 into cells but offer little protection against other coronaviruses, such as the SARS-CoV-1 virus responsible for the severe acute respiratory syndrome outbreak of 2002.

Antibodies that recognize the core region of the spike receptor-binding domain, in contrast, can prevent the entry of various coronaviruses into human cells. Unfortunately, however, individuals exposed to the viral spike protein tend to produce lots of antibodies against the head region but few, if any, antibodies that recognize the core region.

"This suggests that, although the generation of broadly neutralizing antibodies is possible, SARS-CoV-2 infection and current vaccines are unlikely to provide protection against the emergence of novel SARS-related viruses," explains Professor Tomohiro Kurosaki from the WPI Immunology Frontier Research Center at Osaka University in Japan.

"Given that prior coronavirus epidemics such as SARS-CoV-1 and MERS-CoV have occurred due to zoonotic coronaviruses crossing the species barrier, the potential for the emergence of similar viruses in the future poses a significant threat to global public health, even in the face of effective vaccines for current viruses."

Kurosaki and colleagues decided to test a new vaccination strategy that might enable the immune system to produce more broadly neutralizing antibodies.

The researchers genetically engineered the receptor-binding domain of the SARS-CoV-2 spike protein, covering its head region in additional sugar molecules. These sugar molecules could shield the head region from the immune system and boost the production of antibodies against the unshielded core region of the receptor-binding domain.

Indeed, mice immunized with these engineered proteins produced a much higher proportion of antibodies recognizing the core region of the spike protein receptor-binding domain. These antibodies were able to neutralize the cellular entry of not only SARS-CoV-2 but also SARS-CoV-1 and three SARS-like coronaviruses from bats and pangolins.

Much work will need to be done to translate this strategy to humans, but, says Kurosaki, "our data suggest that engineered versions of the spike receptor-binding domain could be a useful component for the development of broadly protective, next-generation vaccines to prevent future coronavirus pandemics."

*Reference: "Glycan engineering of the SARS-CoV-2 receptor-binding domain elicits cross-neutralizing antibodies for SARS-related viruses" 8 October 2021, Journal of Experimental Medicine. DOI: 10.1084/jem.20211003*

***https://wb.md/3BwOW44***

## Adolescents Who Exercised After a Concussion Recovered Faster in RCT

***Resuming aerobic exercise relatively early on – at an intensity that does not worsen symptoms – may help young athletes recover sooner***

**Jake Remaly**

After a concussion, resuming aerobic exercise relatively early on – at an intensity that does not worsen symptoms – may help young athletes recover sooner, compared with stretching, a randomized controlled trial (RCT) shows.

The study adds to emerging evidence that clinicians should prescribe exercise, rather than strict rest, to facilitate concussion

recovery, researchers said.

Tamara McLeod, PhD, ATC, professor and director of athletic training programs at A.T. Still University in Mesa, Ariz., hopes the findings help clinicians see that "this is an approach that should be taken."

"Too often with concussion, patients are given a laundry list of things they are NOT allowed to do," including sports, school, and social activities, said McLeod, who was not involved in the study.

The research, published in The Lancet Child & Adolescent Health, largely replicates the findings of a prior trial while addressing limitations of the previous study's design, researchers said.

For the trial, John J. Leddy, MD, with the State University of New York at Buffalo and colleagues recruited 118 male and female adolescent athletes aged 13-18 years who had had a sport-related concussion in the past 10 days. Investigators at three community and hospital-affiliated sports medicine concussion centers in the United States randomly assigned the athletes to individualized subsymptom-threshold aerobic exercise (61 participants) or stretching exercise (57 participants) at least 20 minutes per day for up to 4 weeks. Aerobic exercise included walking, jogging, or stationary cycling at home.

"It is important that the general clinician community appreciates that prolonged rest and avoidance of physical activity until spontaneous symptom resolution is no longer an acceptable approach to caring for adolescents with concussion," Leddy and coauthors said.

The investigators improved on the "the scientific rigor of their previous RCT by including intention-to-treat and per-protocol analyses, daily symptom reporting, objective exercise adherence measurements, and greater heterogeneity of concussion severity," said Carolyn A. Emery, PhD, and Jonathan Smirl, PhD, both with the University of Calgary (Alta.), in a related commentary. The new study is the first to show that early targeted heart rate subsymptom-threshold aerobic exercise, relative to stretching, shortened recovery time within 4 weeks after sport-related concussion (hazard ratio, 0.52) when controlling for sex, study site, and average daily exercise time, Emery and Smirl said.

A larger proportion of athletes assigned to stretching did not recover by 4 weeks, compared with those assigned to aerobic exercise (32% vs. 21%). The median time to full recovery was longer for the stretching group than for the aerobic exercise group (19 days vs. 14 days).

Among athletes who adhered to their assigned regimens, the differences were more pronounced: The median recovery time was 21 days for the stretching group, compared with 12 days for the aerobic exercise group. The rate of postconcussion symptoms beyond 28 days was 9% in the aerobic exercise group versus 31% in the stretching group, among adherent participants.

More research is needed to establish the efficacy of postconcussion aerobic exercise in adults and for nonsport injury, the researchers noted. Possible mechanisms underlying aerobic exercise's benefits could include increased parasympathetic autonomic tone, improved cerebral blood flow regulation, or enhanced neuron repair, they suggested.

The right amount and timing of exercise, and doing so at an intensity that does not exacerbate symptoms, may be key. Other research has suggested that too much exercise, too soon may delay recovery, Emery said in an interview. "But there is now a lot of evidence to support low and moderate levels of physical activity to expedite recovery," she said.

*The study was funded by the American Medical Society for Sports Medicine. The study and commentary authors and McLeod had no disclosures. This article originally appeared on MDedge.com, part of the Medscape Professional Network.*

https://bit.ly/3oXNeFc

# Italian sailors knew of America 150 years before Christopher Columbus, new analysis of ancient documents suggests

***New analysis of ancient writings suggests that sailors from the Italian hometown of Christopher Columbus knew of America 150 years before its renowned 'discovery'.***

**by Taylor & Francis**

Transcribing and detailing a, circa, 1345 document by a Milanese friar, Galvaneus Flamma, Medieval Latin literature expert Professor Paolo Chiesa has made an "astonishing" discovery of an "exceptional" passage referring to an area we know today as North America. According to Chiesa, the ancient essay—first discovered in 2013—suggests that sailors from Genoa were already aware of this land, recognizable as 'Markland'/ 'Marckalada' – mentioned by some Icelandic sources and identified by scholars as part of the Atlantic coast of North America (usually assumed to be Labrador or Newfoundland).

Published in the peer-reviewed journal *Terrae Incognitae*, the discovery comes ahead of Columbus Day 2021, alternatively celebrated as Indigenous Peoples' Day across many states in the US. The findings add more fuel to the fire for the continuing question of 'what, exactly, did Columbus expect to find when he set out across the ocean?' and come following a period in which his statues have been beheaded, covered with red paint, lassoed around the head and pulled down, set on fire and thrown into a lake.

"We are in the presence of the first reference to the American continent, albeit in an embryonic form, in the Mediterranean area," states Professor Chiesa, from the Department of Literary Studies, Philology and Linguistics at the University of Milan.

Galvaneus was a Dominican friar who lived in Milan and was connected to a family which held at the lordship of the city. He wrote several literary works in Latin, mainly on historical subjects. His testimony is valuable for information on Milanese contemporary facts, about which he has first-hand knowledge.

Cronica universalis, which is analyzed here by Chiesa, is thought to be one of his later works—perhaps the last one—and was left unfinished and unperfected. It aims to detail the history of the whole world, from 'Creation' to when it was published.

In translating and analyzing the document, Professor Chiesa demonstrates how Genoa would have been a "gateway" for news, and how Galvaneus appears to hear, informally, of seafarers' rumors about lands to the extreme north-west for eventual commercial benefit—as well as information about Greenland, which he details accurately (for knowledge of the time).

"These rumors were too vague to find consistency in cartographic or scholarly representations," the professor states, as he explains why Marckalada wasn't classified as a new land at the time.

Regardless though, Chiesa states, Cronica universalis "brings unprecedented evidence to the speculation that news about the American continent, derived from Nordic sources, circulated in Italy one and half centuries before Columbus."

He adds: "What makes the passage (about Marckalada) exceptional is its geographical provenance: not the Nordic area, as in the case of the other mentions, but northern Italy. "The Marckalada described by Galvaneus is 'rich in trees', not unlike the wooded Markland of the Grœnlendinga Saga, and animals live there. "These details could be standard, as distinctive of any good land; but they are not trivial, because the common feature of northern regions is to be bleak and barren, as actually Greenland is in Galvaneus's account, or as Iceland is described by Adam of Bremen."

Overall, Professor Chiesa says, we should "trust" Cronica universalis as throughout the document Galvaneus declares where he has heard of oral stories, and backs his claims with elements

drawn from accounts (legendary or real) belonging to previous traditions on different lands, blended together and reassigned to a specific place.

"I do not see any reason to disbelieve him," states Professor Chiesa, who adds, "it has long been noticed that the fourteenth-century portolan (nautical) charts drawn in Genoa and in Catalonia offer a more advanced geographical representation of the north, which could be achieved through direct contacts with those regions.

"These notions about the north-west are likely to have come to Genoa through the shipping routes to the British Isles and to the continental coasts of the North Sea.

"We have no evidence that Italian or Catalan seafarers ever reached Iceland or Greenland at that time, but they were certainly able to acquire from northern European merchant goods of that origin to be transported to the Mediterranean area.

"The marinarii mentioned by Galvaneus can fit into this dynamic: the Genoese might have brought back to their city scattered news about these lands, some real and some fanciful, that they heard in the northern harbors from Scottish, British, Danish, Norwegian sailors with whom they were trading."

Cronica universalis, written in Latin, is still unpublished; however, an edition is planned, in the context of a scholarly and educational program promoted by the University of Milan.

***More information:*** *Paolo Chiesa, Marckalada: The First Mention of America in the Mediterranean Area (c. 1340), Terrae Incognitae (2021).* DOI: 10.1080/00822884.2021.1943792

***https://bit.ly/3uXWElj***

## Even After Mild COVID-19 Infection, Antibodies Protect From Reinfection for Up to Six Months

***The antibodies' ability to neutralize COVID-19 did not differ significantly over the six-month period.***

A Michigan Medicine study found that most patients with mild COVID-19 infections produce antibodies that persist and protect them from reinfection for up to six months.

Researchers analyzed nearly 130 subjects with PCR-confirmed COVID-19 illness between three and six months after initial infection. Three patients were hospitalized while the rest were treated as outpatients and experienced mild infection, with symptoms including headaches, chills, and loss of taste or smell.

The results, published in *Microbiology Spectrum*, reveal approximately 90% of participants produced spike and nucleocapsid antibody responses, and all but one had persistent antibody levels at follow up.

"Previously, there was a lot of concern that only those with severe COVID-19 produced strong antibody responses to infection," said Charles Schuler, M.D., lead author of the paper and clinical assistant professor of allergy and immunology at Michigan Medicine. "We're showing that people with mild bouts of COVID-19 did really well after their infection, made antibodies, and kept them."

The prospective study's participants were either Michigan Medicine health care workers or patients with a high risk of exposure to COVID-19. Most subjects took part in the same research team's previous study, which found that COVID antibody tests are effective at predicting prior infection.

During the observation period, none of the subjects who produced antibodies were re-infected, compared to 15 antibody-negative patients. Schuler's team also found that the antibodies' ability to neutralize COVID-19 did not differ significantly from the first visit, which occurred three months after infection, to the second visit at the six-month mark.

"While some studies have suggested antibodies against COVID-19 wane over time, these findings provide strong prospective evidence for longer-term immunity for those who produce an immune

response to mild infection," said James Baker Jr., M.D., senior author of the paper and founding director of the Mary H. Weiser Food Allergy Center at Michigan Medicine. "To our knowledge, this is the first prospective study that demonstrates such a risk reduction for clinical reinfection in this specific type of population."

**Impact on COVID vaccination**

The team of researchers is now analyzing samples of this subject group taken up to a year after infection to further evaluate antibody responses. Meanwhile, they concluded that individuals with COVID-19 can delay vaccination for 90 days after infection ends. The Centers for Disease Control and Prevention recommends those treated with monoclonal antibodies or convalescent plasma wait 90 days after receiving treatment before getting vaccinated, and others should wait until they have recovered from COVID-19 and "have met the criteria to discontinue isolation."

A study conducted in Kentucky found that unvaccinated people who already had COVID-19 were 2.34 times more likely than fully vaccinated people to be infected again, suggesting "vaccination provides additional protection against reinfection."

Additionally, the research was conducted between March 2020 and Feb. 2021, months before the highly transmissible Delta variant became the dominant strain of COVID in the United States.

Amid rising cases and hospitalizations, Schuler said, remaining unvaccinated comes with "a high price" for immunity.

"These results are encouraging for those who have already run the gauntlet of COVID-19 infection," he said. "However, I do not recommend citing this study as a reason not to be vaccinated for those never previously infected. Vaccination decreases infectiousness, the risk of hospitalization and deaths from COVID-19, without having the actual infection. Achieving natural immunity by deferring vaccination in favor of infection is not worth going through the discomfort, risk to yourself and risk to others."

*Reference: "Mild SARS-CoV-2 Illness Is Not Associated with Reinfections and Provides Persistent Spike, Nucleocapsid, and Virus-Neutralizing Antibodies" by Charles F. Schuler, IV, Carmen Gherasim, Kelly O'Shea, David M. Manthei, Jesse Chen, Cristyn Zettel, Jonathan P. Troost, Andrew A. Kennedy, Andrew W. Tai, Donald A. Giacherio, Riccardo Valdez, James L. Baldwin and James R. Baker, Jr, 1 September 2021, Microbiology Spectrum. DOI: 10.1128/Spectrum.00087-21*

*Funding: University of Michigan Institutional Funding, COVID-19 Innovation Grant*

***https://bit.ly/3Aub4ea***

## Study Shows Adults Who Stutter Stop if They Think No One Is Listening

***When adults who stutter are on their own and think no one is listening, their stutter suddenly goes away***

**David Nield**

More than 70 million people worldwide are thought to have some kind of stuttering speech impediment – including the current President of the United States – and experts are still continuing to learn more about the condition and what causes it.

Now a new study has revealed something that may give us a big clue into why stuttering happens and how we can treat it: When adults who stutter are on their own and think no one is listening, their stutter suddenly goes away.

And it seems to be that perception of having a listener that's key. What's important about this particular piece of research is that the study participants were convinced that no one was around to hear what they were saying, providing solid scientific evidence for how different scenarios affect the condition.

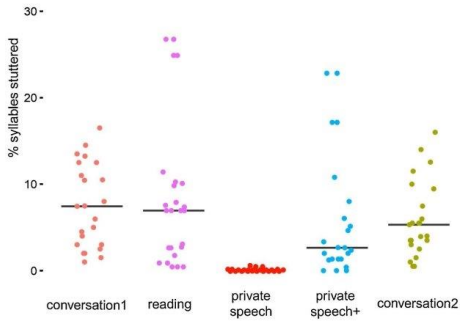
"There is a lot of anecdotal evidence that people who stutter don't stutter when talking alone, but this phenomenon has not been confirmed in the lab, mainly because it's difficult to create conditions in which people believe that they are truly alone," says Eric Jackson, a speech-language pathologist and researcher from

New York University.

The researchers enlisted 23 volunteers and put them through five different scenarios: reading aloud, private speech (the only scenario where it appeared that no one was listening), repeating the private speech for two listeners, and two different conversations with researchers.

For the private speech scenario, the participants were given a trio of challenging computer coding tasks to complete, tasks known to get people talking to themselves in the past. Participants were also told that those who talked out loud while doing the task usually performed better at it.

The volunteers were falsely told that no one would be listening in while they did the computing task, though they were still being monitored and recorded by the researchers. It was the only scenario where stuttering was nearly non-existent across all 23 study participants.




***Stuttering across scenarios.*** **(Jackson et al., Journal of Fluency Disorders, 2021)**

"We developed a novel method to convince participants that they are alone – that their speech wouldn't be heard by a listener – and found that adult stutterers do not stutter under these conditions," says Jackson.

Having been informed afterward that they had been deceived, all of the volunteers agreed to continue with the experiment. The next question is why the lack of an audience has such a significant effect on problems with speech fluency.

That's not something the researchers go into too much detail during this particular study, but they do note that there could be an element of feeling judged or evaluated when there are other people around to listen in.

Stuttering is thought to come about through a combination of genetics and neurophysics. One possible avenue to explore in the future is at what stage social considerations start to affect young children who stutter. "I think this provides evidence that stuttering isn't just a 'speech' problem, but that at its core there must be a strong social component," says Jackson. The research has been published in the *Journal of Fluency Disorders*.

***https://bit.ly/3lwp2Yo***

## Researchers Find Evidence of Link Between Herpes Simplex (Cold Sores) and Neurodegenerative Diseases

***When the protein optineurin, is present in cells it restricts the spread of HSV-1***

A new study by researchers at University of Illinois Chicago suggests that when the protein optineurin, or OPTN, is present in cells it restricts the spread of HSV-1, the herpes simplex virus type 1.

In a “first of its kind” study, researchers also found a potential direct connection between neurodegenerative diseases, such as Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), glaucoma, and the herpesvirus, said Dr. Deepak Shukla, the Marion H. Schenk Esq. Professor in Ophthalmology for Research of the Aging Eye, and vice chair for research at UIC.

The research paper, “OPTN is a host intrinsic restriction factor against neuroinvasive HSV-1 infection,” led by Shukla, was published recently in the journal *Nature Communications.*

Researchers sought to discover why HSV-1 can become fatal for individuals who are immunocompromised but not for healthy individuals. Herpesviruses naturally infect the central nervous system and can result in degenerative brain and eye disorders, as well as encephalitis. However, in most individuals, the virus is suppressed during a primary infection before it can significantly damage the central nervous system.

The new research suggests why HSV-1 is suppressed: OPTN, a conserved autophagy receptor, selectively targets HSV-1 proteins to degradation by autophagy, explained Tejabhiram Yadavalli, a co-author of the study and visiting scholar at UIC's department of ophthalmology and visual science.

"OPTN stops the virus from growing and it stops it by autophagy — engulfing the virus particles inside tiny vesicles called autophagosomes. The autophagy that happens is very selective. That has meaning for other viruses as well," Shukla said.

The researchers believe the results from this study will apply to all eight different human herpesviruses.

For the study, mice with removed OPTN genes were infected with ocular HSV-1. The virus growth was much higher in the brains of animals without OPTN, killing local neurons and eventually leading to animal death. This shows there is a faster degeneration of neurons when OPTN is not there. Additional studies are being planned to examine naturally occurring mutations in OPTN, such as the ones reported in glaucoma and ALS patients, and how they may affect neuronal health and HSV-1 infection, Shukla explained.

"Where you have mutated OPTN plus herpes, you have the recipe to create a disaster in terms of neurodegeneration," Shukla said.

"The study also shows there is an impairment of immune response when there is a deficiency in OPTN. OPTN is needed to signal an influx of proper immune cells at the site of infection. When you don't have it, you have issues," said Chandrashekhar Patil, also a co-author of the study and a visiting scholar at UIC's department of ophthalmology and visual science.

Some of those issues could include neurodegenerative disorders, which researchers believe further research may show.

"We think we will have data to show other viruses, such as Epstein-Barr, Kaposi's sarcoma, varicella-zoster, are all going to share this mechanism because they share homologous proteins," Shukla said.

Because the herpesvirus sits in neurons forever, there is speculation it is connected to neurodegenerative diseases. The immune system requires inflammation to constantly fight off the virus, and neurons have some degree of damage because of this continuous immune response, according to Dr. Tibor Valyi-Nagy, professor of pathology, director of neuropathology at UIC and research collaborator on the study.

The study also showed that animals without OPTN and infected with HSV-1 after 30 days lost the ability to recognize objects. Shukla said this could be an indication that having HSV-1 along with a mutation of OPTN could accelerate neuronal damage, which would translate into cognitive impairment.

"Part of our translational research can be how can we correct the problems with OPTN so that we don't have issues with neurodegeneration," Shukla said.

*Reference: "OPTN is a host intrinsic restriction factor against neuroinvasive HSV-1 infection" by Joshua Ames, Tejabhiram Yadavalli, Rahul Suryawanshi, James Hopkins, Alexander Agelidis, Chandrashekhar Patil, Brian Fredericks, Henry Tseng, Tibor Valyi-Nagy and Deepak Shukla, 13 September 2021, Nature Communications.*

*DOI: 10.1038/s41467-021-25642-z*

*Additional authors are Joshua Ames, Rahul Suryawanshi, James Hopkins, Alexander Agelidis, Chandrashekhar Patil and Brian Fredericks, all of UIC, and Henry Tseng of Duke University Medical Center.*

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