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So-called 'junk' DNA plays a key role in speciation

Study suggests the system of chromosomal organization made possible by satellite DNA is a reason organisms from different species cannot produce viable offspring

by Eva Frederick, Whitehead Institute for Biomedical Research

A new study from Whitehead Institute Member Yukiko Yamashita's lab suggests that the system of chromosomal organization made possible by satellite DNA is one reason that organisms from different species cannot produce viable offspring.

More than 10 percent of our genome is made up of repetitive, seemingly nonsensical stretches of genetic material called satellite DNA that do not code for any proteins. In the past, some scientists have referred to this DNA as "genomic junk."

Over a series of papers spanning several years, however, Whitehead Institute Member Yukiko Yamashita and colleagues have made the case that satellite DNA is not junk, but instead has an essential role in the cell: it works with cellular proteins to keep all of a cell's individual chromosomes together in a single nucleus.

Now, in the latest installment of their work, published online July 24 in the journal *Molecular Biology and Evolution*, Yamashita and former postdoctoral fellow Madhav Jagannathan, currently an assistant professor at ETH Zurich, Switzerland, take these studies a step further, proposing that the system of chromosomal organization made possible by satellite DNA is one reason that organisms from different species cannot produce viable offspring.

"Seven or eight years ago when we decided we wanted to study satellite DNA, we had zero plans to study evolution," said Yamashita, who is also a professor of biology at the Massachusetts Institute of Technology and an investigator with the Howard Hughes Medical Institute.

"This is one very fun part of doing science: when you don't have a preconceived idea, and you just follow the lead until you bump into something completely unexpected."

The origin of species: DNA edition

Researchers have known for years that satellite DNA is highly variable between species. "If you look at the chimpanzee genome and the human genome, the protein coding regions are, like, 98 percent, 99 percent identical," she says. "But the junk DNA part is very, very different."

"These are about the most rapidly evolving sequences in the genome, but the prior perspective has been, "Well, these are junk sequences, who cares if your junk is different from mine?"" said Jagannathan.

But as they were investigating the importance of satellite DNA for fertility and survival in pure species, Yamashita and Jagannathan had their first hint that these repetitive sequences might play a role in speciation.

When the researchers deleted a protein called Prod that binds to a specific satellite DNA sequence in the fruit fly Drosophila melanogaster, the flies' chromosomes scattered outside of the nucleus into tiny globs of cellular material called micronuclei, and the flies died.

"But we realized at this point that this [piece of] satellite DNA that was bound by the Prod protein was completely missing in the nearest relatives of Drosophila melanogaster," Jagannathan said. "It completely doesn't exist. So that's an interesting little problem."

If that piece of satellite DNA was essential for survival in one species but missing from another, it could imply that the two species of flies had evolved different satellite DNA sequences for the same role over time. And since satellite DNA played a role in keeping all the chromosomes together, Yamashita and Jagannathan wondered whether these evolved differences could be one reason different species are reproductively incompatible.

"After we realized the function [of satellite DNA in the cell], the fact that satellite DNA is quite different between species really hit like lightning," Yamashita said. "All of a sudden, it became a completely different investigation."

A tale of two fruit fly species

To study how satellite DNA differences might underlie reproductive incompatibility, the researchers decided to focus on two branches of the fruit fly family tree: the classic lab model Drosophila melanogaster, and its closest relative, Drosophila simulans. These two species diverged from each other two to three million years ago.

Researchers can breed a Drosophila melanogaster female to a Drosophila simulans male, "but [the cross] generates very unhappy offspring," Yamashita said. "Either they're sterile or they die."

Yamashita and Jagannathan bred the flies together, then studied the tissues of the offspring to see what was leading these "unhappy" hybrids to drop like flies. Right away they noticed something interesting: "When we looked at those hybrid tissues, it was very clear that their phenotype was exactly the same as if you had disrupted the satellite DNA [-mediated chromosomal organization] of a pure species," Yamashita said. "The chromosomes were scattered, and not encapsulated in a single nucleus."

Furthermore, the researchers could create a healthy hybrid fly by mutating certain genes in the parent flies called "hybrid incompatibility genes," which have been shown to localize to satellite DNA in the cells of pure species.

Via these experiments, the researchers were able to demonstrate how these genes affect chromosomal packaging in hybrids, and pinpoint the cellular phenotypes associated with them for the first time. "I think for me, that is probably the most critical part of this paper," Jagannathan said.

Taken together, these findings suggest that because satellite DNA mutates relatively frequently, the proteins that bind the satellite DNA and keep chromosomes together must evolve to keep up, leading each species to develop their own "strategy" for working with the satellite DNA. When two organisms with different strategies interbreed, a clash occurs, leading the chromosomes to scatter outside of the nucleus.

In future studies, Yamashita and Jagannathan hope to put their model to the ultimate test: if they can design a protein that can bind the satellite DNA of two different species and hold the chromosomes together, they could theoretically 'rescue' a doomed hybrid, allowing it to survive and produce viable offspring.

This feat of bioengineering is likely years off. "Right now it's just a pure conceptual thing," Yamashita said. "In doing this tinkering, there's probably a lot of specifics that will have to be solved."

For now, the researchers plan to continue investigating the roles of satellite DNA in the cell, armed with their new knowledge of the part it plays in speciation.

"To me, the surprising part of this paper is that our hypothesis was correct," Jagannathan said. "I mean, in retrospect, there are so many ways things could have been inconsistent with what we hypothesized, so it's kind of amazing that we've sort of been able to chart a clear path from start to finish."

More information: *Madhav Jagannathan et al, Defective Satellite DNA Clustering into Chromocenters Underlies Hybrid Incompatibility in Drosophila, Molecular Biology and Evolution (2021). DOI: 10.1093/molbev/msab221*

Madhav Jagannathan et al, Comparative Analysis of Satellite DNA in the Drosophila melanogaster Species Complex, G3 Genes|Genomes|Genetics (2017). DOI: 10.1534/g3.116.035352

Madhav Jagannathan et al, A conserved function for pericentromeric satellite DNA, eLife (2018). DOI: 10.7554/eLife.34122

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Journal information: *Molecular Biology and Evolution , eLife*

https://wb.md/3BfqvYa

Plastic Barriers May Not Stop COVID-19 Spread, Experts Say

May not help, and in fact, could make the situation worse by blocking normal air flow

Carolyn Crist

Plastic barriers that separate people in stores, restaurants, and classrooms may not be as effective at stopping the spread of COVID-19 as originally thought, according *to The New York Times.* Scientists who study air flow, ventilation and aerosol droplets say the barriers may not help, and in fact, could make the situation worse by blocking normal air flow, the newspaper reported.

Typically, as people interact and breathe in a room, currents and ventilation systems recirculate the air and disperse the exhaled particles. With plastic barriers, however, particles could get trapped in "dead zones" and build up.

"If you have a forest of barriers in a classroom, it's going to interfere with proper ventilation of that room," Linsey Marr, professor of civil and environmental engineering at Virginia Tech, told the newspaper. "Everybody's aerosols are going to be trapped and stuck there and building up, and they will end up spreading beyond your own desk," she said.

Several variables factor into the efficacy of plastic barriers, *The New York Times* reported. Shields may stop big respiratory droplets from coughs and sneezes, for instance, but they may not do much to prevent small aerosol particles from viruses such as COVID-19 from spreading.

"We have shown this effect of blocking larger particles, but also that the smaller aerosols travel over the screen and become mixed in the room air within about five minutes," Catherine Noakes, a professor of environment engineering at the University of Leeds, told the newspaper. "This means if people are interacting for more than a few minutes, they would likely be exposed to the virus regardless of the screen," she said.

The effectiveness of plastic barriers likely also depends on the location and setup, the newspaper reported. A bus driver with a large barrier, for instance, may be able to avoid inhaling the particles that passengers are exhaling. A bank cashier or store clerk behind a large barrier may also be partly protected.

Even still, scientists say more research is needed. For instance, taller barriers are more likely to be effective. However, a large number of barriers in one room could likely block air flow.

Researchers have recommended that schools and offices focus on ventilation, masks, and vaccines to slow the spread of the coronavirus.

"Air flow in rooms is pretty complicated," Richard Corsi, dean of engineering at the University of California at Davis, told the newspaper. "Every room is different in terms of the arrangement of furniture, the height of the walls and ceilings, the vents, where the bookshelves are," he said. "All of these things have a huge impact on the actual flow and air distribution in a room."

Source: *The New York Times: "Those Anti-Covid Plastic Barriers Probably Don't Help and May Make Things Worse."*

https://go.nature.com/3BdEFt4

So much ice is melting that Earth's crust is moving

As the continents' frozen burden dissipates, the ground deforms — not only in the immediate area, but also in far-flung locations.

The loss of melting ice from land masses such as Greenland and Antarctica is causing the planet's crust to warp slightly, even in spots more than 1,000 kilometres from the ice loss.

Ice melt removes mass from Earth's continents. Liberated from the overlying weight, land that was once covered by ice lifts up. This vertical response has been much studied, but Sophie Coulson at Harvard University in Cambridge, Massachusetts, and her

colleagues wanted to analyse how the ground shifts horizontally. They gathered satellite data on ice loss from Greenland, Antarctica, mountain glaciers and ice caps, and combined them with a model of how Earth's crust responds to changes in mass.

Between 2003 and 2018, ice melting from Greenland and from Arctic glaciers caused the ground to shift horizontally across much of the Northern Hemisphere, and by as much as 0.3 millimetres a year in much of Canada and the United States. In some areas, even far from the melting ice, the horizontal movement was greater than the vertical movement. *Geophys. Res. Lett.* (2021)

https://bit.ly/3mGNRSq

This Wasp Nest of Mine, I'm Gonna Let It Shine

Under ultraviolet light, the silk that covers the base of paper-wasp nests turns neon green.

By Katherine J. Wu

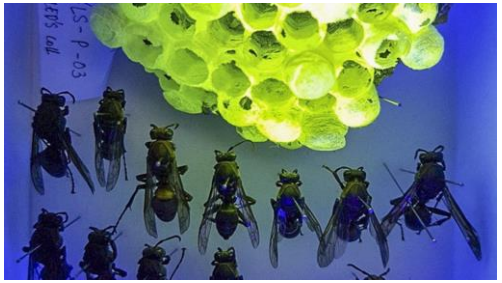
On a muggy spring night in 2016, the chemist Bernd Schöllhorn was tromping alone through a forest in northern Vietnam. Into the inky darkness, he raised a black light—and saw an extraordinarily bright shape winking at him in eerie shades of yellowish green.

"I thought it was somebody else," Schöllhorn, a researcher at the University of Paris, told me. But when he cut his own light, the stranger's torch instantly extinguished as well. Schöllhorn pushed his way through the vegetation until he reached the source of the glow: a geometric, open-combed nest of a paper-wasp colony.

"It was just incredible," Schöllhorn recalled. Bathed in ultraviolet rays from his flashlight, the nest looked as though it had been dipped in a vat of highlighter ink, so bright and Day-Glo green that the inches-wide structure was visible from some 60 feet away. The wasps' home, Schöllhorn realized, was fluorescing, as though prepping for an entomological rave. And he had no idea why.

Over the next several years, Schöllhorn and his colleagues searched for paper wasps in other parts of Vietnam, then in France and French Guiana, until they'd found nests from six different species in the genus *Polistes*. When fed a steady stream of ultraviolet rays, all of the nests glowed, each with a bit of regional flair: The four from Vietnam all pulsed in green, while the other two, from Europe and South America, were a more muted teal-ish blue. "Finding this in so many species, and across three different continents, is remarkable," Swanne Gordon, an evolutionary biologist at Washington University in St. Louis, who studies insect signaling and wasn't involved in the study, told me.

The wasps themselves didn't light up; neither did the topmost parts of the nests, constructed out of chewed-up wood (hence the "paper" moniker). The glow, the researchers found, came from a layer of silk stitched across the openings of the hexagonal cells at each nest's base.



Bernd Schöllhorn and Serge Berthier

Scientists hadn't pinpointed this silk as fluorescent before. Its primary purpose is to cocoon young paper wasps during their metamorphosis, when larvae "dissolve their bodies" and reform themselves into adults, Sara Miller, a paper-wasp expert at Cornell University, told me. What's inside the sealed cell is "really like a bag of mush," Miller said. The larvae excrete silk out of a gland, and it shields the pupa from the ravages of reality—predators, pathogens, harsh weather conditions—much like a chrysalis protects a butterfly-to-be.

In the light of the forest, when viewed with human eyes, paper-wasp silk appears whitish or yellowish and is decidedly matte. But when fed ultraviolet light in the lab, the string-like fibers convert those rays into a fluorescence funky enough for an '80s aerobics ensemble.

Especially staggering was the silk's capacity for shine. In the lab, Schöllhorn's team calculated each nest's quantum yield, or its capacity to emit light when fed a certain number of photons. "Those kinds of measurements are tricky to get," especially from flora and fauna, Carlos Taboada, who studies glowy amphibians at Duke University, told me.

The few quantum yields that researchers have managed to glean from fluorescent animals tend to fall between 0.3 and 12.5 percent; a few years ago, Taboada uncovered frogs that shone near the top of that range. The brightest nest the researchers collected, a *Polistes brunetus* creation from Vietnam, registered a whopping 35 percent. "That is incredibly large for a biological tissue," Taboada, who wasn't involved in the new study, said.

The silk's beguiling glow, the researchers confirmed, falls in the range of wavelengths that wasp eyes can see. "They're very sensitive to green," Schöllhorn told me. But it's not yet clear what purpose the fluorescence serves for the insects, if any at all. Plenty of things will glow under black lights, if given the chance. That doesn't guarantee that these glimmers are more than a coincidence of physics.

"It's still possible this is just an incidental by-product of how the silk is made," Liz Tibbetts, a paper-wasp expert at the University of Michigan who wasn't involved in the study, told me.

Schöllhorn and his colleagues haven't yet figured out whether the silk's glow-stick effect is important to the wasps, or exactly how the larvae cook it up. The fluorescent molecules could be dietary, for instance, or entirely of the insects' own making.

Still, Schöllhorn thinks the glow probably has *some* role to play. One possibility is that it serves as a sort of psychedelic beacon for work-weary wasps staggering back home. Several of the insect experts I talked with were a little hesitant to embrace this idea, because paper wasps, which are famously detail-oriented, are already ace at navigation. The silk is also ablaze for only part of the nesting cycle, after eggs had been laid and hatched.

A more intriguing hypothesis, experts told me, might hinge on the silk's ability to safeguard pupae by waylaying harmful, DNA-damaging UV rays—a sort of DIY sunscreen for baby wasps. "To me, that's the most appealing idea," Floria Mora-Kepfer Uy, a wasp expert at the University of Rochester who wasn't involved in the study, told me. That could come in handy, she said, for nests that hang at the edges of forests, where the vegetation is sparse and the structures are constantly flooded with sunlight.

But Uy also told me that she hasn't yet seen evidence of fluorescence in the nests she's studied in the subtropics of North and Central America.

Scientists have known for years about bony fish, sharks, worms, jellies, corals, and other marine creatures that light up to attract mates, lure prey, or discombobulate predators. The list of terrestrial examples is sparse, but is growing: Frogs, salamanders, birds, spiders, butterflies, and even flying squirrels all bat for Team Glow. Paper-wasp silk could provide yet more clues about fluorescence's function on land.

Humans perceive the world "in just one way," Tibbetts told me. "We're walking around with blinders on." Terrestrial fluorescence might not be so rare at all; we just haven't been searching for it.

Schöllhorn is one of many researchers trying to course-correct—which is why he originally took that fateful black-light-wielding walk in Vietnam. Many of these excursions are solo trips, he told me. "No one wanted to go with me," he said. "There is no light at all, and snakes, spiders, insects everywhere." He's gotten used to it, though, and the rewards are always worth the trek.

The next great glower won't be found unless someone is willing to look.

https://bit.ly/3Dmhhv5

Ants use soil physics to excavate metre-long tunnels that last decades

Ant colonies can descend several metres underground, house millions of insects and last for decades, despite being made without the benefit of machinery and reinforcing material.

By Matthew Sparkes

The secrets of these impressive architectural structures are being revealed by three-dimensional X-ray imaging and computer simulations, and could be used to develop robotic mining machines. José Andrade at the California Institute of Technology and his colleagues set up miniature ant colonies in a container holding 500 millilitres of soil and 15 western harvester ants (*Pogonomyrmex occidentalis*). The position of every ant and every grain of soil was then captured by high-resolution X-ray scans every 10 minutes for 20 hours.

The X-ray results gave researchers exact details about the shape of each tunnel and which grains were being removed to create it. The team then created a computer model using those scans to understand the forces acting upon the tunnels. The size, shape and orientation of every grain was recreated in the model and the direction and size of force on each grain could be calculated, including gravity, friction and cohesion caused by humidity. The model was accurate to the 0.07 millimetre resolution of the scanner.

The results suggest that forces within the soil tend to wrap around the tunnel axis as ants excavate, forming what the team call "arches" in the soil that have a greater diameter than the tunnel itself. This reduces the load acting on the soil particles within the arches, where the ants are constructing their tunnel. As a result, the ants can easily remove these particles to extend the tunnel without causing cave-ins. The arches also make the tunnel stronger and more durable.

"We had naively thought that ants perhaps were playing Jenga, that they were tapping, maybe they were wiggling grains, maybe they were even grabbing the grains of least resistance," says Andrade. He says it is now clear that the ants appear to know nothing about forces and show no signs of decision-making, but instead follow a very simple behavioural algorithm that has evolved over time.

The ants tend to dig relatively straight tunnels that descend at the angle of repose – the slope at which a granular material naturally forms mounds – which was around 40 degrees in this case. They also pick exactly the right grains to remove to create a protective arch above.

"In a remarkable way – in a rather, you know, serendipitous way – they've stumbled upon a technique for digging that is in line with the laws of physics, but incredibly efficient," says Andrade.

The team believes that if the behavioural algorithm can be further analysed and ultimately replicated, then it may find application in automated mining robots, either here on Earth or on other planetary bodies where the already risky business of mining would be even more dangerous for humans.

Journal reference: Proceedings of the National Academy of Sciences, DOI: 10.1073/pnas.2102267118

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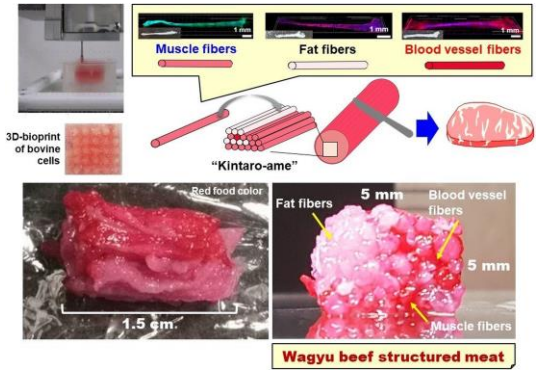
First 3D-bioprinted structured Wagyu beef-like meat

3D-printing a meat alternative containing muscle, fat, and blood vessels arranged to resemble steaks

Scientists from Osaka University used stem cells isolated from Wagyu cows to 3D-print a meat alternative containing muscle, fat, and blood vessels arranged to closely resemble conventional steaks. This work may help usher in a more sustainable future with widely available cultured meat. Wagyu can be literally translated into "Japanese cow," and is famous around the globe for its high content

of intramuscular fat, known as marbling or sashi. This marbling provides the beef its rich flavors and distinctive texture.

However, the way cattle are raised today is often considered to be unsustainable in light of its outsized contribution to climate emissions. Currently, the available "cultured meat" alternatives only consist primarily of poorly organized muscle fiber cells that fail to reproduce the complex structure of real beef steaks.



Credit: Osaka University

Now, a team of scientists led by Osaka University have used 3D-Printing to create synthetic meat that looks more like the real thing. "Using the histological structure of Wagyu beef as a blueprint, we have developed a 3D-printing method that can produce tailor-made complex structures, like muscle fibers, fat, and blood vessels," lead author Dong-Hee Kang says. To overcome this challenge, the team started with two types of stem cells, called bovine satellite cells and adipose-derived stem cells. Under the right laboratory conditions, these "multipotent" cells can be coaxed to differentiate into every type of cell needed to produce the cultured meat.

Individual fibers including muscle, fat, or blood vessels were fabricated from these cells using bioprinting. The fibers were then arranged in 3D, following the histological structure, to reproduce the structure of the real Wagyu meat, which was finally sliced perpendicularly, in a similar way to the traditional Japanese candy Kintaro-ame. This process made the reconstruction of the complex meat tissue structure possible in a customizable manner. "By improving this technology, it will be possible to not only reproduce complex meat structures, such as the beautiful sashi of Wagyu beef, but to also make subtle adjustments to the fat and muscle components," senior author Michiya Matsusaki says. That is, customers would be able to order cultured meat with their desired amount of fat, based on taste and health considerations.

More information: *Dong-Hee Kang et al, Engineered whole cut meat-like tissue by the assembly of cell fibers using tendon-gel integrated bioprinting, Nature Communications (2021). DOI: 10.1038/s41467-021-25236-9*

https://bit.ly/3jirilc

Geneticists map the rhinoceros family tree

Solving a question going back to Darwin's time about the relationships among the world's five living rhinoceros species

There's been an age-old question going back to Darwin's time about the relationships among the world's five living rhinoceros species. One reason answers have been hard to come by is that most rhinos went extinct before the Pleistocene.

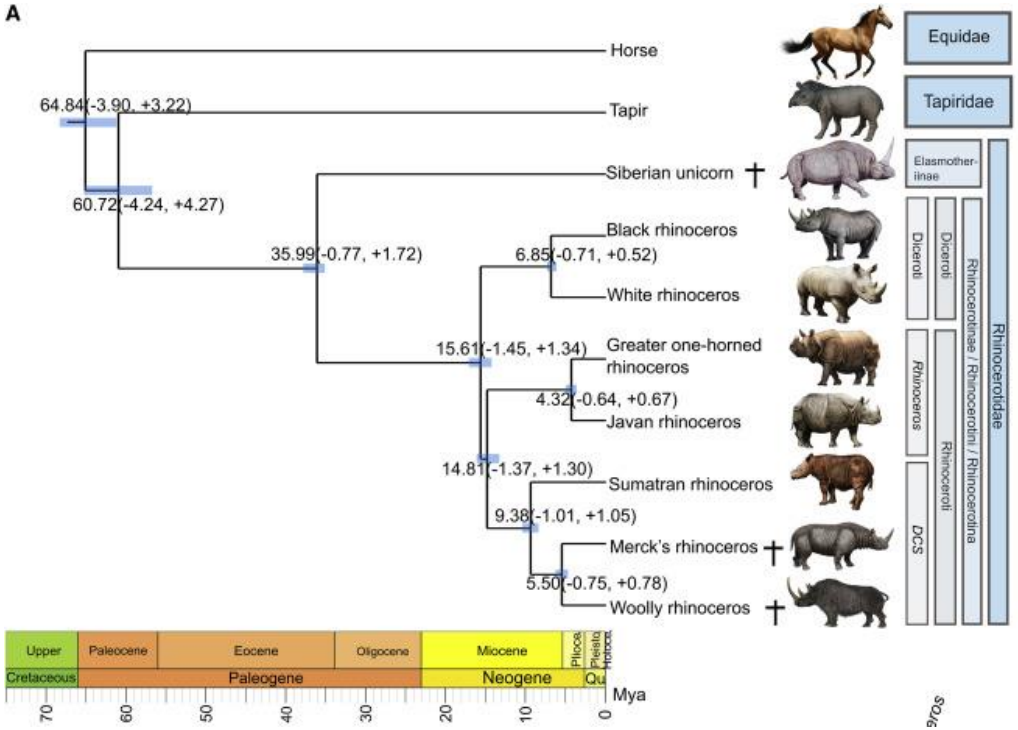
This illustration shows a paleoartist's reconstruction of the three extinct rhinoceros species whose genomes were sequenced as part of the study. In the foreground is a Siberian unicorn (Elasmotherium sibiricum), and close behind are two Merck's rhinoceroses (Stephanorhinus kirchbergensis). In the far background is a woolly rhinoceros (Coelodonta antiquitatis). **Credit: Beth Zaiken**

Now, researchers reporting in the journal *Cell* on August 24 have helped to fill the gaps in the rhino evolutionary family tree by analyzing genomes of all five living species together with the genomes of three ancient and extinct species.

The findings show that the oldest split separated African and Eurasian lineages about 16 million year ago. They also find that—while dwindling populations of rhinos today have lower genetic diversity and more inbreeding than they did in the past—

rhinoceroses have historically had low levels of genetic diversity.

"We can now show that the main branch in the rhinoceroses' tree of life is among geographic regions, Africa versus Eurasia, and not between the rhinos that have one versus two horns," says Love Dalén of the Centre for Palaeogenetics and the Swedish Museum of Natural History. "The second important finding is that all rhinoceroses, even the extinct ones, have comparatively low genetic diversity. To some extent, this means that the low genetic diversity we see in present-day rhinos, which are all endangered, is partly a consequence of their biology.



(A) Dated species tree of the Rhinocerotidae based on a consensus of trees generated every 100 kb across the genome using maximum likelihood methods and multiple fossil calibrations as detailed in STAR Methods. Blue horizontal bars show 95% confidence intervals of estimated divergence dates between lineages. Black crosses indicate extinct species.

"All eight species generally displayed either a continual but slow decrease in population size over the last 2 million years, or continuously small population sizes over extended time periods," said Mick Westbury of the University of Copenhagen, Denmark. "Continuously low population sizes may indicate that rhinoceroses in general are adapted to low levels of diversity."

This notion is consistent with an apparent lack of accumulated deleterious mutations in rhinos in recent decades. Westbury says that rhinos may have purged deleterious mutations in the last 100 years, allowing them to remain relatively healthy, despite low genetic diversity.

The new study was inspired at a scientific meeting. Dalén and Tom Gilbert, University of Copenhagen, had been working separately on different rhino species. They realized that if they joined forces, along with colleagues around the world, they could do a comparative study of all living rhinos together with the three species that went extinct during the last Ice Age.

There were some challenges to overcome, says Shanlin Liu, China Agricultural University, Beijing. "When we decided to put together all the rhinoceroses' data and conduct a comparative genomics study, we also confronted the 'big data' problem," Liu explained.

The genome data represented different data types, in part due to the inclusion of both modern and ancient DNA. The team had to develop new analysis tools to take those differences into account. The new approaches and tools they developed can now be applied to studies in other taxonomic groups.

Dalén says that the findings are "partly good news, and partly not." It appears that low levels of genetic diversity in rhinos is part of their long-term history and hasn't led to an increase in health problems related to inbreeding and disease-causing mutations.

"However, we also find that present-day rhinos have lower genetic diversity, and higher levels of inbreeding, compared to our

historical and prehistoric rhinoceros genomes," he says. "This suggests that recent population declines caused by hunting and habitat destruction have had an impact on the genomes. This is not good, since low genetic diversity and high inbreeding may increase the risk of extinction in the present-day species."

The findings do have some practical implications for rhino conservation, the re-searchers say.

"Now we know that the low diversity we see in contemporary individuals may not be indicative of an inability to recover, but instead a natural state of rhinoceros," Westbury says. "We can better guide recovery programs to focus on increasing population size rather than individual genetic diversity."

The team hopes that the new findings will be useful for continued study of rhinoceroses and their conservation. Dalén reports that his team is now working on a more in-depth study of the extinct woolly rhinoceros. Meanwhile, Westbury is involved in comparing the genomes of African black rhinoceros sampled from before the recent decrease in population size to those of contemporary individuals.

"We hope that this will provide a framework to better understand where translocated populations may have arisen from, direct changes in genetic diversity, and whether any populations may have been lost forever because of humans," Westbury said.

More information: *Cell, Liu et al.: "Ancient and modern genomes unravel the evolutionary history of the rhinoceros family" www.cell.com/cell/fulltext/S0092-8674(21)00891-6 , DOI: 10.1016/j.cell.2021.07.032*

https://nyti.ms/2WvhnQk

A Shifting Climate Gave Humans Many Opportunities to Leave Africa

A new paleoclimate model finds many favorable windows when Homo sapiens might have survived a migration out of Africa.

By Sabrina Imbler

A cast of the skull of Herto Man, a 160,000 to 154,000-year-old human specimen discovered in Ethiopia in 1997. **Credit... imageBROKER/Alamy**

Until recently, scientists believed modern humans left Africa in one enormous exodus around 65,000 years ago. But a new climate model suggests that modern humans had several windows of opportunity to leave the continent far earlier.

The research, published Tuesday in the journal Nature Communications, reconstructed the climate of northeastern Africa over the last 300,000 years. The scientists identified when there would have been enough rainfall to allow a group of hunter-gatherers to survive the journey to the Arabian Peninsula.

Archaeological and genetic data still support the idea that all non-African people descended from a single migration that left the continent between 50,000 and 80,000 years ago. But the new paper bolsters the theory that Homo sapiens had multiple migrations out of Africa.

Even if various groups succeeded in leaving the continent, they may not each have played a large role in populating the world. An earlier constellation of fossils, some with contested dating, highlights some of Homo sapiens's false starts: part of a middle finger from 85,000 years ago, found in Arabia; a human jawbone from at least 177,000 years ago, found in Israel; a skull from possibly 210,000 years ago, found in Greece.

It is inviting to extrapolate the timing and paths of these early journeys from these archaeological records. But the fossils offer "limited, rather gappy lines of evidence" of possible migrations, said Andrea Manica, an evolutionary ecologist at the University of Cambridge and an author on the new paper. Dr. Manica believes an

ecological model could tackle the question from a new angle: first predict what would have been possible, then see if the fossils line up.

"It's an intriguing question to ask whether there were environmental thresholds for those earlier dispersals, even though those dispersals may have been limited or short-lived," said Rick Potts, a paleoanthropologist who directs the Human Origins Program at the Smithsonian National Museum of Natural History.

"The new paper grasps the important thing," said Dr. Potts, who was not involved with the research. "There were multiple instances of our species' dispersal beyond Africa prior to the main one."

Jessica Tierney, a paleoclimatologist at the University of Arizona who also was not involved with the research, said she found the approach interesting but inconclusive. "Ultimately this is a model, not geology or archaeology," Dr. Tierney said. "The mystery remains until you have better and more paleoenvironmental records."

Dr. Manica and Robert Beyer, a researcher at the Potsdam Institute for Climate Impact Research in Germany, first devised their ecological approach in 2018. Scientists had already modeled the climate as far back as 125,000 years, but Dr. Manica and Dr. Beyer wanted to go back to the date of the earliest anatomically modern human fossils, which were found in Morocco and are estimated to be at least 300,000 years old.

"That's the moment when you see our species actually existed," Dr. Manica said. Mario Krapp, a research fellow at Antarctica New Zealand and an author on the paper, developed an emulator for the existing climate model to go back deeper into time.

To predict when Homo sapiens feasibly could have moved through northeastern Africa and the Arabian Peninsula, the researchers needed to find out the absolute minimal conditions in which humans could survive. "We wanted to build up this catalog of the good times and bad times," Dr. Manica said.

They looked at distribution maps of present-day hunter-gatherers and found that human populations are generally not recorded in areas where precipitation falls below 3.5 inches of rain per year. Rainfall this trifling is not enough to sustain green patches of reeds, grasses and shrubs that feed the grazing animals that early humans may have depended on.

Once the researchers set the threshold of survivability at 3.5 inches, they overlaid their climate reconstructions to see when conditions might have been sweet enough to travel through two possible routes into Eurasia: the Sinai Peninsula up north and, further south, the Strait of Bab-el-Mandeb , which separates the Horn of Africa from contemporary Yemen.

Their model revealed a handful of historical windows during which there was enough rainfall and relatively low sea levels to sustain a human migration out of Africa. The Sinai land bridge was crossable several times, as early as 246,000 years ago, and the southern strait had even more favorable windows, including the period 65,000 years ago.

The sheer number of crossing opportunities surprised Dr. Manica, given the robust evidence suggesting that only the recent mass exodus had peopled the world with Homo sapiens. "I was hoping, maybe naïvely, that period would just be perfect, where everything was right," Dr. Manica said. "But everything was right before as well. Several times, for a matter of fact."

So the question still stands: If some Homo sapiens were able to colonize Eurasia far earlier, why were they not successful?

The researchers have some theories. If early humans could have moved out of Africa much earlier, they would have faced stiff competition from other early human species; the north was a Neanderthal stronghold, and much of East Asia was likely populated by another extinct human lineage, the Denisovans. The

models also suggest that dry periods often followed the favorable windows, which could have isolated any populations undertaking an exodus. But the authors also note that even if times were good and wet, humans may not have taken advantage of these periods to migrate out.

The model had to make several assumptions, including that the southern strait would always have been crossable by humans and that those people might have had the boat technology to make the crossing. The model breaks down the geography of the region to a grid with a resolution with half a degree latitude and longitude, or around 30 miles. This approach inevitably ignores the mosaic of vegetation and topography that exists on the ground.

Dr. Tierney, the paleoclimatologist, said the new paper's climate models were too simple to predict what climate change was like hundreds of thousands of years ago. She also questioned some of the rules of the model, such as humans only being able to migrate alongside a minimum level of rainfall. "I guess it makes sense to make that assumption," Dr. Tierney said. "On the other hand, the Nile River is always there. They could move out that way almost any time."

Similarly, Emily Beverly, an earth scientist at the University of Houston who was not involved with the research, said the authors did not consider the existence of freshwater springs that could have served as a source of potable water for migrating humans during dry periods.

On the other hand, Dr. Potts, the paleoanthropologist, noted that the minimum level of rainfall in the model would have been "far too low" to allow hunter-gatherers to successfully disperse out of Africa. Dr. Potts pointed to previous research suggesting that early humans could only have dispersed in the continent when the mean average rainfall was more than 3.9 inches per year, and typically dispersed when there was at least 10 inches of rain. The more interesting research question, in Dr. Potts' eyes, is what dispersal paths would have been available in these windows of more abundant rainfall.

Perhaps the largest question still remains unanswered. "More and more evidence suggests we did this multiple times," Dr. Beverly said. "The question I'm always left with is, Why?"

Abdullah Alsharekh, an archaeologist at King Saud University in Riyadh, Saudi Arabia, who was not involved with the research, said he appreciated the paper's examination of the prehistoric Arabian climate. "The last couple of decades have shown that many of our questions about out-of-Africa models can be greatly enhanced by more on-the-ground research in Arabia," Dr. Alsharekh wrote in an email. "What lies beneath those sandy deserts?"

Dr. Manica has a similar hope, that future archaeological excavations and genetic investigations will shed more light on Homo sapiens's staggered foray out of Africa: both the earlier, seemingly unsuccessful waves and the main migration that unleashed Homo sapiens to irrevocably alter the rest of the world.

https://bit.ly/3DpruqQ

Like Venom Coursing Through the Body: Mechanism Driving COVID-19 Mortality Identified

Researchers have identified what may be the key molecular mechanism responsible for COVID-19 mortality – an enzyme related to neurotoxins found in rattlesnake venom.

An enzyme with an elusive role in severe inflammation may be a key mechanism driving COVID-19 severity and could provide a new therapeutic target to reduce COVID-19 mortality, according to a study published in the *Journal of Clinical Investigation*.

Researchers from the University of Arizona, in collaboration with Stony Brook University and Wake Forest University School of Medicine, analyzed blood samples from two COVID-19 patient cohorts and found that circulation of the enzyme – secreted

phospholipase A2 group IIA, or sPLA2-IIA – may be the most important factor in predicting which patients with severe COVID-19 eventually succumb to the virus.

sPLA2-IIA, which has similarities to an active enzyme in rattlesnake venom, is found in low concentrations in healthy individuals and has long been known to play a critical role in defense against bacterial infections, destroying microbial cell membranes.

When the activated enzyme circulates at high levels, it has the capacity to "shred" the membranes of vital organs, said Floyd (Ski) Chilton, senior author on the paper and director of the UArizona Precision Nutrition and Wellness Initiative housed in the university's College of Agriculture and Life Sciences.

"It's a bell-shaped curve of disease resistance versus host tolerance," Chilton said. "In other words, this enzyme is trying to kill the virus, but at a certain point it is released in such high amounts that things head in a really bad direction, destroying the patient's cell membranes and thereby contributing to multiple organ failure and death."

Together with available clinically tested sPLA2-IIA inhibitors, "the study supports a new therapeutic target to reduce or even prevent COVID-19 mortality," said study co-author Maurizio Del Poeta, a SUNY distinguished professor in the Department of Microbiology and Immunology in the Renaissance School of Medicine at Stony Brook University.

Collaboration Amid Chaos

"The idea to identify a potential prognostic factor in COVID-19 patients originated from Dr. Chilton," Del Poeta said. "He first contacted us last fall with the idea to analyze lipids and metabolites in blood samples of COVID-19 patients."

Del Poeta and his team collected stored plasma samples and went to work analyzing medical charts and tracking down critical clinical data from 127 patients hospitalized at Stony Brook University between January and July 2020. A second independent cohort included a mix of 154 patient samples collected from Stony Brook and Banner University Medical Center in Tucson between January and November 2020.

"These are small cohorts, admittedly, but it was a heroic effort to get them and all associated clinical parameters from each patient under these circumstances," Chilton said. "As opposed to most studies that are well planned out over the course of years, this was happening in real time on the ICU floor."

The research team was able to analyze thousands of patient data points using machine learning algorithms. Beyond traditional risk factors such as age, body mass index and preexisting conditions, the team also focused on biochemical enzymes, as well as patients' levels of lipid metabolites.

"In this study, we were able to identify patterns of metabolites that were present in individuals who succumbed to the disease," said lead study author Justin Snider, an assistant research professor in the UArizona Department of Nutrition. "The metabolites that surfaced revealed cell energy dysfunction and high levels of the sPLA2-IIA enzyme. The former was expected but not the latter."

Using the same machine learning methods, the researchers developed a decision tree to predict COVID-19 mortality. Most healthy individuals have circulating levels of the sPLA2-IIA enzyme hovering around half a nanogram per milliliter. According to the study, COVID-19 was lethal in 63% of patients who had severe COVID-19 and levels of sPLA2-IIA equal to or greater than 10 nanograms per milliliter.

"Many patients who died from COVID-19 had some of the highest levels of this enzyme that have ever been reported," said Chilton, who has been studying the enzyme for over three decades.

An Enzyme with a Bite

The role of the sPLA2-IIA enzyme has been the subject of study for half of a century and it is “possibly the most examined member of the phospholipase family,” Chilton explained.

Charles McCall, lead researcher from Wake Forest University on the study, refers to the enzyme as a “shredder” for its known prevalence in severe inflammation events, such as bacterial sepsis, as well as hemorrhagic and cardiac shock.

Previous research has shown how the enzyme destroys microbial cell membranes in bacterial infections, as well as its similar genetic ancestry with a key enzyme found in snake venom.

The protein “shares a high sequence homology to the active enzyme in rattlesnake venom and, like venom coursing through the body, it has the capacity to bind to receptors at neuromuscular junctions and potentially disable the function of these muscles,” Chilton said.

“Roughly a third of people develop long COVID, and many of them were active individuals who now can’t walk 100 yards. The question we are investigating now is: If this enzyme is still relatively high and active, could it be responsible for part of the long COVID outcomes that we’re seeing?”

Reference: “Group IIA Secreted Phospholipase A2 is Associated with the Pathobiology Leading to COVID-19 Mortality” by Justin M. Snider, Jeehyun Karen You, Xia Wang, Ashley J. Snider, Brian Hallmark, Manja M. Zec, Michael C. Seeds, Susan Sergeant, Laurel Johnstone, Qiuming Wang, Ryan Sprissler, Tara F. Carr, Karen Lutrick, Sairam Parthasarathy, Christian Bime, Hao H. Zhang, Chiara Luberto, Richard R. Kew, Yusuf A. Hannun, Stefano Guerra, Charles E. McCall, Guang Yao, Maurizio Del Poeta and Floyd H. Chilton, 24 August 2021, Journal of Clinical Investigation. DOI: 10.1172/JCI149236

https://wb.md/3Dm4yZq

Human Brain Patterns May Help Build a Better AI System

Artificial intelligence (AI)–powered neural networks modeled on real human brain connectivity patterns perform cognitive tasks better than traditional AI systems, new research suggests.

Megan Brooks

"This work opens new opportunities to discover how the network organization of the brain optimizes cognitive capacity," write the researchers from The Neuro (Montreal Neurological Institute-Hospital) and the Quebec Artificial Intelligence Institute, Quebec, Canada.

Senior investigator Bratislav Misic, PhD, said the research has potential clinical application for studying diseases of the brain, which is something his team is actively working on.

"For example, using MRI techniques, we can measure different patterns of atrophy in neurodegenerative diseases such as Alzheimer's disease," Misic told *Medscape Medical News*.

"We can use these disease patterns from real patients to artificially lesion these connectomes and to ask how a particular disease causes a particular pattern of symptoms and cognitive deficits," he added.

The findings were published online August 9 in *Nature Machine Intelligence*.

Unique Approach

Using brain imaging data, the investigators reconstructed a human brain connectivity pattern and applied it to an artificial neural network (ANN).

After training, the ANN successfully performed a working memory task more flexibly and efficiently than other "benchmark" AI systems.

The researchers note that their approach is unique because previous work on brain connectivity, also known as connectomics, has focused on describing brain organization without regard to how it actually functions.

Traditional ANNs have arbitrary structures that do not reflect how real brain networks are organized. Integrating brain connectomics into the construction of ANNs can reveal how the wiring of the brain supports specific cognitive skills, the investigators write.

"Up until now, if you look at how neural networks are constructed,

the architectures that are used are very ad hoc and very problem specific," Misic said.

"But the connectomics revolution that's happened in neuroscience over the past 20 years or so has given us the ability to really measure and trace out connection patterns in a variety of organisms, including the human brain," Misic added.

He noted that the researchers took wiring patterns of the real human brain and implemented it as an ANN. They then "trained that network to perform a very simple cognitive task, and when you compare it to other benchmark architectures, it actually does better," he said.

This shows that there is "something fundamentally different about how the human brain is wired up and that the design principles that we can see in the human brain could be used to potentially build better artificial networks," Misic concluded.

Funding for the research was provided by the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains, Healthy Lives initiative, and by the Natural Sciences and Engineering Research Council of Canada, Fonds de Recherche du Quebec – Santé, the Canadian Institute for Advanced Research, Canada Research Chairs, Fonds de Recherche du Quebec – Nature et Technologies, and the Centre UNIQUE (Union of Neuroscience and Artificial Intelligence). The investigators have reported no relevant financial relationships.

Nat Mach Intell. Published online August 9, 2021. Abstract

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

A plundered pterosaur reveals the extinct flyer's extreme headgear

A seized fossil reveals the full glory of a winged reptile from the age of the dinosaurs.

When police busted a fossil-smuggling operation at Brazil's largest port, they recovered six yellowish limestone slabs — in which the nearly complete remains of an extinct winged reptile called a pterosaur were embedded. What's more, this pterosaur species was formerly known only from skulls.

Victor Beccari at the University of São Paulo, Brazil, and his colleagues identified the ancient contraband as *Tupandactylus navigans*, which lived more than 100 million years ago. Soft tissue rarely fossilizes, but the specimen boasts soft-tissue remains of nearly all of the reptile's imposing head crest, which is five times taller than its skull. The fossil also reveals the animal's large blade-shaped chin crest.

The pterosaur's forelimbs would have unfolded to an impressive 2.7-metre wingspan. The presence of a structure called a notarium, which braces the skeleton against the considerable forces generated by wing-flapping, shows that the animal almost certainly flew.

A newly described fossil of the pterosaur Tupandactylus navigans (artist's impression) preserves the soft tissue of its huge head crest, which might have made it clumsier in the air. **Credit: Victor Beccari**

But its long neck and forelimbs, and its cumbersome crest, hint that it flew only for short distances. Much of its time might have been spent foraging on the ground, as if it were a massive chicken.

PLoS ONE (2021)

https://bit.ly/3mCjxIN

Oldest genome from Wallacea shows previously unknown ancient human relations

Portions of the genome did not match these groups. This brings new surprises about the evolution of modern humans.

The oldest genome of a modern human from the Wallacea region—the islands between western Indonesia and Papua New Guinea—indicates a previously undescribed ancient human relationship. Researchers were able to isolate sufficient genetic material from the skull of an individual buried more than 7,000 years ago on the Indonesian island of Sulawesi. It belonged to a hunter-gatherer

society and was interred at the site now called Leang Panninge ('Bat Cave'). A large part of the genetic code matched that of today's Papua New Guineans and Aboriginal Australians. Yet portions of the genome did not match these groups. This brings new surprises about the evolution of modern humans.

The international study was accomplished through close collaboration with several researchers and institutions from Indonesia. It was headed by Professor Johannes Krause of the Max Planck Institutes for Evolutionary Anthropology in Leipzig and the Science of Human History in Jena, Professor Cosimo Posth of the Senckenberg Centre for Human Evolution and Palaeoenvironment at the University of Tübingen, and Professor Adam Brumm of Griffith University, Australia. The study has been published in the latest edition of *Nature*.

Almost completely preserved skeleton

The Wallacean Islands formed stepping stones in the spread of the first modern humans from Eurasia to Oceania, probably more than 50,000 years ago. Archaeological finds show that the ancestors of our species lived in Wallacea as early as 47,000 years ago. Yet few human skeletons have been found. One of the most distinctive archaeological discoveries in this region is the Toalean technology complex, dated to a much more recent period between 8,000 and 1,500 years ago. Among the objects manufactured by the people of the Toalean culture are the characteristic stone arrowheads known as Maros points. The Toalean culture has only been found in a relatively small area on the southern peninsula of Sulawesi. "We were able to assign the burial at Leang Panninge to that culture," says Adam Brumm. "This is remarkable since it is the first largely complete and well preserved skeleton associated with the Toalean culture."

Selina Carlhoff, doctoral candidate at the Max Planck Institute for the Science of Human History and lead author of the study, isolated DNA from the petrous bone of the skull. "It was a major challenge, as the remains had been strongly degraded by the tropical climate," she says. The analysis showed that the Leang Panninge individual was related to the first modern humans to spread to Oceania from Eurasia some 50,000 years ago. Like the genome of the indigenous inhabitants of New Guinea and Australia, the Leang Panninge individual's genome contained traces of Denisovan DNA. The Denisovans are an extinct group of archaic humans known primarily from finds in Siberia and Tibet. "The fact that their genes are found in the hunter-gatherers of Leang Panninge supports our earlier hypothesis that the Denisovans occupied a far larger geographical area," says Johannes Krause.

Another piece in the great genetic puzzle

A comparison with genomic data of hunter-gatherers who lived west of Wallacea at about the same time as the Leang Panninge individual provided further clues—that data showed no traces of Denisovan DNA. "The geographic distribution of Denisovans and modern humans may have overlapped in the Wallacea region. It may well be the key place where Denisova people and the ancestors of indigenous Australians and Papuans interbred," says Cosimo Posth.

Stone arrowheads, known as Maros points, are up to 8,000 years old. They are considered typical of the Toalean techno-complex developed by the people living in the south of the island of Sulawesi. **Credit: Yinika L Perston**

However, the Leang Panninge individual also carries a large proportion of its genome from an ancient Asian population. "That came as a surprise, because we do know of the spread of modern humans from eastern Asia into the Wallacea region—but that took place far later, around 3,500 years ago. That was long after this

individual was alive," Johannes Krause reports. Furthermore, the research team has found no evidence that the group Leang Panninge belonged to left descendants among today's population in Wallacea. It remains unclear what happened to the Toalean culture and its people. "This new piece of the genetic puzzle from Leang Panninge illustrates above all just how little we know about the genetic history of modern humans in southeast Asia," Posth says.

More information: *Genome of a middle Holocene hunter-gatherer from Wallacea, Nature (2021).* *DOI: 10.1038/s41586-021-03823-6* , *www.nature.com/articles/s41586-021-03823-6*

https://bit.ly/3qJHom1

Johnson & Johnson booster shot increases antibodies to coronavirus nine-fold, company says

Will health officials recommend J&J recipients to receive a booster dose?

By Yasemin Saplakoglu

A booster dose of Johnson & Johnson's COVID-19 vaccine prompted a big spike in antibodies among clinical trial participants, when taken six to eight months after the first dose, the company announced on Wednesday (Aug.25).

Health officials have recommended that people vaccinated with the Moderna or Pfizer-BioNTech vaccines receive a booster dose about eight months after their second dose, due to waning immunity, Live Science previously reported. But they have not yet recommended a booster for the Johnson & Johnson vaccine, citing the lack of data.

"We also anticipate booster shots will likely be needed for people who received the Johnson & Johnson (J&J) vaccine," the U.S. Department of Health and Human services said in a statement on Aug.18. They added that they expect more data on the Johnson & Johnson booster shots in the next few weeks, and that they will "keep the public informed with a timely plan for J&J booster shots as well."

More than 14 million people in the U.S. received the single-dose Johnson & Johnson vaccine. Today's data, taken from clinical trial participants, suggests that a booster may be beneficial.

A booster dose of the Johnson & Johnson vaccine generated a nine-fold increase in antibodies compared to the level seen 28 days after the initial dose, the company reported in a statement. The data is based on two small clinical trials conducted in the U.S. and in Europe, and the company submitted the results, which haven't yet been peer-reviewed, to the preprint database medRxiv.

"We have established that a single shot of our COVID-19 vaccine generates strong and robust immune responses that are durable and persistent through eight months," Dr. Mathai Mammen, the Global Head of Janssen Research & Development at Johnson & Johnson, said in the statement. "With these new data, we also see that a booster dose of the Johnson & Johnson COVID-19 vaccine further increases antibody responses among study participants who had previously received our vaccine."

Mammen added that they will discuss potential strategies for booster doses with public health officials.

But the study looked at antibody levels and not at real-world efficacy, so it's not clear if people who get the booster shot will be less likely to be infected or to develop severe disease than those who don't, according to CNN. Still, experts are reaching a consensus that antibody levels may be indicative of the amount of immune protection, according to CNN.

Experts told NPR that while the studies were small, and didn't look at real-world protection, the findings would likely support the idea of giving booster shots to those who received the Johnson & Johnson vaccine. "It is pointing toward the utility of a second dose. I think that's reasonable," Saad Omer, a vaccine researcher at Yale told NPR.

https://bit.ly/3mIRd7u

A Big Step Forward in the Search for Alien Life: New Class of Exoplanet Very Different to Our Own

Astronomers have identified a new class of habitable planets, dubbed 'Hycean' planets – hot, ocean-covered planets with hydrogen-rich atmospheres

A new class of exoplanet very different to our own, but which could support life, has been identified by astronomers, which could greatly accelerate the search for life outside our Solar System.

In the search for life elsewhere, astronomers have mostly looked for planets of a similar size, mass, temperature, and atmospheric composition to Earth. However, astronomers from the University of Cambridge believe there are more promising possibilities out there.

The researchers have identified a new class of habitable planets, dubbed 'Hycean' planets – hot, ocean-covered planets with hydrogen-rich atmospheres – which are more numerous and observable than Earth-like planets.

The researchers say the results, reported in *The Astrophysical Journal*, could mean that finding biosignatures of life outside our Solar System within the next two or three years is a real possibility.

"Hycean planets open a whole new avenue in our search for life elsewhere," said Dr. Nikku Madhusudhan from Cambridge's Institute of Astronomy, who led the research.

Many of the prime Hycean candidates identified by the researchers are bigger and hotter than Earth, but still have the characteristics to host large oceans that could support microbial life similar to that found in some of Earth's most extreme aquatic environments.

These planets also allow for a far wider habitable zone, or 'Goldilocks zone', compared to Earth-like planets. This means that they could still support life even though they lie outside the range where a planet similar to Earth would need to be in order to be habitable.

Thousands of planets outside our Solar System have been discovered since the first exoplanet was identified nearly 30 years ago. The vast majority are planets between the sizes of Earth and Neptune and are often referred to as 'super-Earths' or 'mini-Neptunes': they can be predominantly rocky or ice giants with hydrogen-rich atmospheres, or something in between.

Most mini-Neptunes are over 1.6 times the size of Earth: smaller than Neptune but too big to have rocky interiors like Earth. Earlier studies of such planets have found that the pressure and temperature beneath their hydrogen-rich atmospheres would be too high to support life.

However, a recent study on the mini-Neptune K2-18b by Madhusudhan's team found that in certain conditions these planets could support life. The result led to a detailed investigation into the full range of planetary and stellar properties for which these conditions are possible, which known exoplanets may satisfy those conditions, and whether their biosignatures may be observable.

The investigation led the researchers to identify a new class of planets, Hycean planets, with massive planet-wide oceans beneath hydrogen-rich atmospheres. Hycean planets can be up to 2.6 times larger than Earth and have atmospheric temperatures up to nearly 200 degrees Celsius, but their oceanic conditions could be similar to those conducive for microbial life in Earth's oceans. Such planets also include tidally locked 'dark' Hycean worlds that may have habitable conditions only on their permanent night sides, and 'cold' Hycean worlds that receive little radiation from their stars.

Planets of this size dominate the known exoplanet population, although they have not been studied in nearly as much detail as super-Earths. Hycean worlds are likely quite common, meaning that the most promising places to look for life elsewhere in the Galaxy may have been hiding in plain sight.

However, size alone is not enough to confirm whether a planet is

Hycean: other aspects such as mass, temperature, and atmospheric properties are required for confirmation.

When trying to determine what the conditions are like on a planet many light-years away, astronomers first need to determine whether the planet lies in the habitable zone of its star, and then look for molecular signatures to infer the planet's atmospheric and internal structure, which govern the surface conditions, presence of oceans and potential for life.

Astronomers also look for certain biosignatures which could indicate the possibility of life. Most often, these are oxygen, ozone, methane, and nitrous oxide, which are all present on Earth. There are also a number of other biomarkers, such as methyl chloride and dimethyl sulfide, that are less abundant on Earth but can be promising indicators of life on planets with hydrogen-rich atmospheres where oxygen or ozone may not be as abundant.

"Essentially, when we've been looking for these various molecular signatures, we have been focusing on planets similar to Earth, which is a reasonable place to start," said Madhusudhan. "But we think Hycean planets offer a better chance of finding several trace biosignatures."

"It's exciting that habitable conditions could exist on planets so different from Earth," said co-author Anjali Piette, also from Cambridge.

Madhusudhan and his team found that a number of trace terrestrial biomarkers expected to be present in Hycean atmospheres would be readily detectable with spectroscopic observations in the near future. The larger sizes, higher temperatures, and hydrogen-rich atmospheres of Hycean planets make their atmospheric signatures much more detectable than Earth-like planets.

The Cambridge team identified a sizeable sample of potential Hycean worlds which are prime candidates for detailed study with next-generation telescopes, such as the James Webb Space Telescope (JWST), which is due to be launched later this year. These planets all orbit red dwarf stars between 35-150 light-years away: close by astronomical standards. Planned JWST observations of the most promising candidate, K2-18b, could lead to the detection of one or more biosignature molecules.

"A biosignature detection would transform our understanding of life in the universe," said Madhusudhan. "We need to be open about where we expect to find life and what form that life could take, as nature continues to surprise us in often unimaginable ways."

Reference: "Habitability and Biosignatures of Hycean Worlds" 25 August 2021, The Astrophysical Journal.DOI: 10.3847/1538-4357/abfd9c

https://nyti.ms/3Bh3pjY

Heart Problem More Common After Covid-19 Than After Vaccination, Study Finds

The research did not assess the risks specifically for young males, who are the most likely to develop the rare side effect.

By Emily Anthes and Noah Weiland

The Pfizer-BioNTech Covid-19 vaccine is associated with an increased risk of myocarditis, an inflammation of the heart muscle, a large new study from Israel confirms. But the side effect remains rare, and Covid-19 is more likely to cause myocarditis than the vaccine is, scientists reported on Wednesday.

The research, which is based on the electronic health records of about two million people who are 16 or older, provides a comprehensive look at the real-wold incidence of various adverse events after both vaccination and infection with the coronavirus.

Although the study did not break down the myocarditis risks by age or by sex, the median age of people who developed the condition after vaccination was 25, and 19 of the 21 cases were in males, the researchers reported.

In addition to myocarditis, the Pfizer vaccine was also associated

with an increased risk of swollen lymph nodes, appendicitis and shingles, although all three side effects remained uncommon in the study. Coronavirus infection was not associated with these side effects, but it did increase the odds of several potentially serious cardiovascular problems, including heart attacks and blood clots.

“Coronavirus is very dangerous, and it’s very dangerous to the human body in many ways,” said Ben Reis, a co-author of the new study and the director of the predictive medicine group at the Boston Children’s Hospital Computational Health Informatics Program.

He added, “If the reason that someone so far has been hesitating to get the vaccine is fear of this very rare and usually not very serious adverse event called myocarditis, well, this study shows that that very same adverse event is actually associated with a higher risk if you’re not vaccinated and you get infected.”

The data arrived in the middle of an intense discussion among federal regulators about the risks of myocarditis and pericarditis, which is inflammation of the lining around the heart, in younger recipients of both the Pfizer-BioNTech and the Moderna vaccines, concerns that very likely led the Food and Drug Administration to negotiate larger pediatric trials with the vaccine makers this summer in the hopes of adequately assessing the risks before a possible emergency authorization for younger children. The companies are studying lower dosing in children to alleviate some of the risk.

In their review of the Pfizer-BioNTech vaccine, regulators paid close attention to an American health care claims database, which found that the risk of the conditions in 16- and 17-year-old vaccinated boys could be as high as 1 in 5,000. The cases in the database were unconfirmed, the F.D.A. cautioned in an analysis published this week, but they were considered a reasonable estimate of the possible risk. Even in the worst-case scenarios of post-vaccination myocarditis and pericarditis modeled by the F.D.A., the benefits of vaccination still outweighed the risks, the analysis said.

The study was one reason the F.D.A. said this week that after its licensure of Pfizer-BioNTech’s vaccine, Pfizer would conduct studies of myocarditis and pericarditis risks in people who received the shot, including long-term outcomes for those who fall ill after vaccination.

Israel’s vaccination campaign, which relied on the Pfizer vaccine, got off to a fast start; by May 24, nearly five million people, or roughly 55 percent of the nation’s population, had received both doses of the vaccine.

The new study, which was published in the New England Journal of Medicine, is based on an analysis of the electronic health records of Clalit Health Services, the nation’s largest H.M.O.

The researchers assembled a group of roughly 880,000 people, age 16 or older, who had been vaccinated by May 24. To create a control group, they matched each of those individuals to an unvaccinated person who was medically and demographically similar. “You can think about them as pseudo twins,” said Dr. Ran Balicer, the chief innovation officer for Clalit Health Services and the lead author of the new study.

Then the researchers calculated the incidence of 25 different potential adverse events in each group. In a second round of analysis, they calculated the incidence of the same potential side effects in a group of 170,000 people who had tested positive for the coronavirus and in a similar group of uninfected controls.

They found that although myocarditis remained rare, it was more common in the vaccinated group than the unvaccinated one. There were an extra 2.7 cases of myocarditis for every 100,000 people in the vaccinated group, compared with the unvaccinated one, the researchers found. But the risks were even higher among those who had contracted the virus. There were an extra 11 cases of the

condition for every 100,000 people who had been infected with the coronavirus, compared with those who had not.

The study provides critical context for understanding the risks and benefits of vaccination, said Dr. Brian Feingold, an expert on heart inflammation in children at the UPMC Children's Hospital of Pittsburgh who said he fields calls from parents who are concerned about the myocarditis risk. "And nobody's blowing that off, but I think you just have to look at that in context," he said. "Those risks related to Covid are higher than the risks related to the vaccine."

In addition to myocarditis, coronavirus infection was also associated with an increased risk of heart attacks, irregular heart beat, blood clots in the lungs or legs, kidney injury and bleeding inside the skull. For every 100,000 infections, there were an extra 25 heart attacks and 62 cases of blood clots in the lungs, for instance.

"When you try to make your decision on whether or not you should take the vaccine, one of the things to ask is not only what are the potential adverse events associated with taking the vaccine, but also what am I risking when I think about Covid-19 as the other option," Dr. Balicer said.

Although the study is reassuring, it is important to continue collecting data on the myocarditis risks in young males in particular, scientists said.

"But we're at this red hot moment," said Dr. Sean O'Leary, a pediatric infectious disease expert at the University of Colorado Anschutz Medical Campus. "This is what we've got, and the benefits still consistently appear to greatly outweigh the risks."

In one recent study, which has not yet been published in a peer reviewed journal, researchers calculated that 12- to 17-year-old boys were about six times as likely to develop myocarditis after infection with the virus than after receiving one of the mRNA vaccines.

https://bit.ly/3zs9n13

Actinium's ionic radius revised after decades

Chemistry of one of Earth's rarest elements remains mysterious, though not for lack of trying

By Kit Chapman

The ionic radius of actinium(III) may be far smaller and closer to the lanthanides than the most recent measurements from the 1950s and 70s suggest, a review by researchers at Lawrence Livermore National Laboratory, US, has found. This could have potential ramifications for cancer therapies.

Actinium-225 glows blue because the alpha particles it emits ionise the surrounding air **Source: © Oak Ridge National Laboratory**

Actinium was discovered by French chemist André-Louis Debierne in 1899. But it exists in such small quantities naturally – usually from the radioactive decay of heavier elements – that it can't be extracted and used in experiments. Instead, researchers rely on actinium created in nuclear reactors. Even so, the element is often in short supply, with only microgram quantities available to a handful of teams around the world.

This means experimentalists have to be selective in the research they perform, often relying on data from earlier work. This is why much of the element's chemistry remains a mystery. Now, a group led by Gauthier Deblonde at Livermore's Seaborg Institute has taken a forensic approach to previous data, predominantly crystallography during the 1950s and 1970s, comparing it with more recent x-ray absorption experiments.

The results suggest the ionic radius has been overestimated by 0.06Å, a significant distance for an actinide. This, Deblonde and colleagues conclude, is likely due to the complexity of working with of actinium – which has few spectroscopic features, is

colourless, not fluorescent and diamagnetic, as well as incredibly short-lived – and the probable contamination of the sample with traces of radium.

The review is particularly important given actinium-225's increasing promise as an anti-cancer therapy. Complexes of actinium with a chelating dodecane tetraacetic acid ligand (Dota) are being investigated in several types of cancer. 'This correction very nicely explains why the actinium cation fits into the cavity of Dota ligand, for which it is supposed to be too large,' says Ekaterina Dadachova, a pharmacy researcher at the University of Saskatchewan, Canada, who specialises in radiotherapies. 'It also helps to explain why actinium was 'slipping out' of the grip of many macrocyclic ligands specifically designed for it.'

While actinium-225 is considered an important potential therapy, it's not the only actinium isotope that's found a use; actinium-227 is essential as a precursor to radium-223, a chemotherapy agent approved in more than 50 countries. In 2018, the US Department of Energy entered into a 10-year commercial agreement with Bayer to supply the pharma giant with the isotope from its reactor facility at Oak Ridge National Laboratory.

'This article demonstrates cross-pollination of ideas between radiopharmaceutical chemistry and classical inorganic chemistry with radiotherapeutic work renewing the interest in inorganic chemistry of actinium,' Dadachova adds. 'The information emanating from the inorganic chemistry field will help to design better chelating agents and better therapies.'

Justin Wilson, who studies radioactive metal complexes in medicine at Cornell University, US, agrees. 'The revised ionic radius put forth in this study will be of significant value to the research community, especially in light of the very promising therapeutic properties of actinium-225.' With the modern spectroscopic equipment now available, Wilson adds, 'it is likely that we will learn much about this elusive element'.

References *G J-P Deblonde, M Zavarin and A B Kersting, Coord. Chem. Rev., 2021,* ***446****, 214130 (DOI: 10.1016/j.ccr.2021.214130)*

https://bit.ly/2Y8Ut1V

How Migraines Protect Against Type 2 Diabetes

People who get migraines are less likely to develop type 2 diabetes, while some people who develop diabetes become less prone to migraines.

Today, scientists studying the link between these conditions report how the peptides that cause migraine pain can influence production of insulin in mice, possibly by regulating the amount of secreted insulin or by increasing the number of pancreatic cells that produce it. These findings could improve methods to prevent or treat diabetes.

The researchers will present their results at the fall meeting of the American Chemical Society (ACS). ACS Fall 2021 is a hybrid meeting being held virtually and in-person August 22-26, and on-demand content will be available August 30-September 30. The meeting features more than 7,000 presentations on a wide range of science topics.

The link between the two diseases isn't obvious: "Migraines happen in the brain, while diabetes is associated with the pancreas, and these organs are far from each other," says Thanh Do, Ph.D., the project's principal investigator. His group became interested in the subject after a number of papers described an inverse relationship between the conditions.

Researchers already knew that two peptides in the nervous system — calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) — play a major role in causing the pain of migraines. These same peptides, along with the related peptide amylin, are also found in the pancreas. There, they influence release of insulin from beta cells.

Insulin regulates blood sugar levels by helping other cells in the body absorb glucose and either store it or use it for energy. In type 2 diabetes, those other cells become resistant to insulin and less capable of absorbing glucose, leading to high blood sugar levels. The beta cells initially compensate by ramping up insulin production but eventually wear themselves out and die, exacerbating the issue.

Because of their role in migraine and diabetes, CGRP and PACAP offer targets for therapies that could treat either of these conditions. Migraine drugs that interfere with CGRP and its cellular receptors recently went on the market, and other treatments are being studied. Yet, more research is needed to clarify the peptides' effects. Do is trying to clear up contradictory findings about their impact on insulin.

To probe the peptides' activity in mice, Do's University of Tennessee group devised a method to glean data from just a few hundred beta cells. They recently reported that this technique showed that CGRP lowered levels of mouse insulin 2, the analog of human insulin. This may counter the insulin resistance that develops in type 2 diabetes, Do says. But CGRP was less effective at regulating mouse insulin 1, which agrees with early studies showing that mice with only insulin 1 are prone to developing diabetes.

The disease is also associated with aggregation of amylin, says Aleksandra Antevska, a graduate student in Do's lab who is presenting the work at the meeting. These aggregates may contribute to the beta cell damage that helps cause type 2 diabetes, Do notes. Because amylin and insulin are co-secreted by beta cells, using CGRP to limit insulin production could also limit amylin production, he says. That could protect the cells and help normalize their function.

PACAP, too, is thought to play a protective role against type 2 diabetes. That's confusing since PACAP has been shown to stimulate insulin release, which leads to insulin resistance, Do says. His team is now trying to resolve this conundrum. The group's initial findings show that PACAP's actions could depend on glucose levels. The team has found preliminary evidence that PACAP regulates insulin in a glucose-dependent manner and promotes beta cell proliferation, rather than prodding existing beta cells to work harder — thus avoiding the risk of wearing out the existing cells. They are developing analytical methods to test this.

"Despite these positive results, you can't inject CGRP and PACAP into the body as therapeutic strategies for diabetes because these peptides cause migraine pain," Do says. "But once we understand how they exert their effects on insulin secretion, we can design peptide analogs that would control insulin but would not bind to the pain receptor."

Because CGRP and PACAP can seemingly protect against diabetes, Do and others worry that the anti-CGRP and anti-PACAP treatments under development or already on the market for migraine could have the unintended consequence of increasing the risk of diabetes. In addition, these peptides are involved in numerous other beneficial functions in the body, such as blood vessel dilation. So Do and other scientists are also exploring the potential risks of altering the peptides' activity.

Recorded media briefing on this topic **25:35**

The researchers acknowledge support and funding from the University of Tennessee.

https://bit.ly/3sZHGKG

"Inescapable" COVID-19 Antibody Discovery – Neutralizes All Known SARS-CoV-2 Strains

An antibody therapy that appears to neutralize all known SARS-CoV-2 strains, and other coronaviruses, was developed with a little help from structural biologist Jay Nix.

Lifesaving COVID-19 vaccines are allowing us to feel optimistic

again, after more than a year of anxiety and tragedy. But vaccines are only one side of the coin – we also need treatments that can prevent severe disease after someone has been infected. In the past year, there has been significant progress in developing effective antibody-based therapies, and three drugs are currently available through emergency use authorization (EUA) by the Food and Drug Administration.

Sotrovimab, the newest antibody therapy, was developed by GlaxoSmithKline and Vir Biotechnology after a large collaborative study by scientists from across the nation discovered a natural antibody (in the blood of a SARS survivor, back in 2003) that has remarkable breadth and efficacy.

Experiments showed that this antibody, called S309, neutralizes all known SARS-CoV-2 strains – including newly emerged mutants that can now "escape" from previous antibody therapies – as well as the closely related original SARS-CoV virus.

Jay Nix, leader of the Molecular Biology Consortium based at Berkeley Lab's Advanced Light Source (ALS), used beamlines at the ALS and beamlines at SLAC's Stanford Synchrotron Radiation Lightsource to perform X-ray crystallography on samples of survivor-derived antibodies during an early phase of the study.

His work, alongside other crystallography and cryo-electron microscopy findings, helped generate detailed structural maps of how these antibodies bind to the SARS-CoV-2 spike protein, allowing the wider team to select the most promising contenders and advance them to cell culture- and animal-based studies. Following exciting lab results, the developers designed sotrovimab based on the structure of S309, and evaluated it in clinical trials.

The FDA granted an EUA for sotrovimab in late May after trials showed that people with mild to moderate COVID-19 infections who received an infusion of the therapy had an 85% reduction in rates of hospitalization or death, compared with placebo.

But the team didn't stop there.

Understanding that new mutations could arise and that a novel pathogenic coronavirus could emerge from an animal-human crossover event, the scientists began a follow-up study to deeply explore what factors make antibodies resistant to viral escape and how certain antibodies are also broadly reactive against diverse, related viruses. Using biochemical and structural analysis, deep mutational scanning, and binding experiments, they identified one antibody with unparalleled universal potency.

"This antibody, which binds to a previously unknown site on the coronavirus spike protein, appears to neutralize all known sarbecoviruses – the genus of coronaviruses that cause respiratory infections in mammals," said Nix, who is an affiliate in Berkeley Lab's Biosciences Area. "And, due to the unique binding site on mutation-resistant part of the virus, it may well be more difficult for a new strain to escape."

Subsequent tests in hamsters suggest that this antibody could even prevent a COVID-19 infection if given prophylactically. The new work was published in *Nature*.

Reference: "SARS-CoV-2 RBD antibodies that maximize breadth and resistance to escape" by Tyler N. Starr, Nadine Czudnochowski, Zhuoming Liu, Fabrizia Zatta, Young-Jun Park, Amin Addetia, Dora Pinto, Martina Beltramello, Patrick Hernandez, Allison J. Greaney, Roberta Marzi, William G. Glass, Ivy Zhang, Adam S. Dingens, John E. Bowen, M. Alejandra Tortorici, Alexandra C. Walls, Jason A. Wojcechowskyj, Anna De Marco, Laura E. Rosen, Jiayi Zhou, Martin Montiel-Ruiz, Hannah Kaiser, Josh Dillen, Heather Tucker, Jessica Bassi, Chiara Silacci-Fregni, Michael P. Housley, Julia di Iulio, Gloria Lombardo, Maria Agostini, Nicole Sprugasci, Katja Culap, Stefano Jaconi, Marcel Meury, Exequiel Dellota, Rana Abdelnabi, Shi-Yan Caroline Foo, Elisabetta Cameroni, Spencer Stumpf, Tristan I. Croll, Jay C. Nix, Colin Havenar-Daughton, Luca Piccoli, Fabio Benigni, Johan Neyts, Amalio Telenti, Florian A. Lempp, Matteo S. Pizzuto, John D. Chodera, Christy M. Hebner, Herbert W. Virgin, Sean P. J. Whelan, David Veesler, Davide Corti, Jesse D. Bloom and Gyorgy Snell, 14 July 2021, Nature.
DOI: 10.1038/s41586-021-03807-6

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https://wb.md/3zGJkn3

Children's Upper Airways Primed to Combat SARS-CoV-2 Infection

Upper airways of children are pre-activated and primed to detect SARS-CoV-2 infection: may contribute to stronger early immune responses

Megan Brooks

Epithelial and immune cells of the upper airways of children are pre-activated and primed to detect SARS-CoV-2 infection, which may contribute to stronger early immune responses to SARS-CoV-2 infection than adults, new research suggests.

The findings may help to explain why children have a lower risk of developing severe COVID-19 illness or becoming infected with SARS-CoV-2 in the first place, the researchers say.

The study was published online August 18 in *Nature Biotechnology*.

Primed for Action

Children appear to be better able than adults to control SARS-CoV-2 infection, but, until now, the exact molecular mechanisms have been unclear.

A team of investigators from Germany did an in-depth analysis of nasal swab samples obtained from 24 children and 21 adults who tested positive for SARS-CoV-2, as well as a control group of 18 children and 23 adults who tested negative for SARS-CoV-2.

"We wanted to understand why viral defense appears to work so much better in children than in adults," Irina Lehmann, PhD, head of the molecular epidemiology unit at the Berlin Institute of Health Charité – Universitätsmedizin Berlin, explained in a news release.

Single-cell sequencing showed that children had higher baseline levels of certain RNA-sensing receptors that are relevant to SARS-CoV-2 detection, such as MDA5 and RIG-I, in the epithelial and immune cells of their noses.

This differential expression led to stronger early immune responses to SARS-CoV-2 infection in children than in adults.

Children were also more likely than adults to have distinct immune cell subpopulations, including *KLRC1*+ cytotoxic T cells, involved in fighting infection, and memory CD8+ T cells, associated with the development of long-lasting immunity.

"Clear Evidence"

The study provides "clear evidence" that upper airway immune cells of children are "primed for virus sensing, resulting in a stronger early innate antiviral response to SARS-CoV-2 infection than in adults," the investigators say.

Primed virus sensing and a pre-activated innate immune response in children leads to efficient early production of interferons (IFNs) in the infected airways, likely mediating substantial antiviral effects, they note.

Ultimately, this may lead to lower viral replication and faster clearance in children. In fact, several studies have already shown that children eliminate the virus quicker than adults, consistent with the concept that they shut down viral replication earlier, the study team says.

Weighing in on the findings for *Medscape Medical News*, John Wherry, PhD, director of the Institute for Immunology at the University of Pennsylvania, Philadelphia, said this "interesting study highlights potential differences in innate immunity and possibly geographic immunity in the upper respiratory tract in children versus adults."

"We know there are differences in innate immunity over a lifespan but exactly how these differences might relate to viral infection remains unclear," said Wherry, who was not involved in the study.

"Children, of course, often have more respiratory infections than adults (but) whether this is due to exposure (ie, daycare, schools, etc) or susceptibility (lack of accumulated adaptive immunity over a greater number of years of exposure) is unclear," Wherry noted.

"These data may help reveal what kinds of innate immune responses in the upper respiratory tract might help restrain SARS-CoV-2 and (perhaps partially) explain why children typically have milder COVID-19 disease," he added.

The study was supported by the Berlin Institute of Health COVID-19 research program and fightCOVID@DKFZ initiative, European Commission, German Federal Ministry for Education and Research (BMBF), and German Research Foundation. Lehmann and Wherry have reported no relevant financial relationships.

Nat Biotechnol. Published online August 18, 2021. Full text

https://bit.ly/3kA4fSd

The invasive emerald ash borer has destroyed millions of trees – scientists aim to control it with tiny parasitic wasps

Few people ever actually see the insect itself – just the trail of destruction it leaves behind

Kristine Grayson *

The emerald ash borer (*Agrilus planipennis*) is a deceptively attractive metallic-green adult beetle with a red abdomen. But few people ever actually see the insect itself – just the trail of destruction it leaves behind under the bark of ash trees.

Adult emerald ash borer beetles are about 0.5 inches long. **PA DEC, CC BY**

These insects, which are native to Asia and Russia, were first discovered in Michigan in 2002. Since then they have spread to 35 states and become the most destructive and costly invasive wood-boring insect in U.S. history. They have also been detected in the Canadian provinces of Ontario, Quebec, Manitoba, New Brunswick and Nova Scotia.

In 2021 the U.S. Department of Agriculture stopped regulating the movement of ash trees and wood products in infested areas because the beetles spread rapidly despite quarantine efforts. Now federal regulators and researchers are pursuing a different strategy: biological control. Scientists think that tiny parasitic wasps, which prey on emerald ash borers in their native range, hold the key to curbing this invasive species and returning ash trees to North American forests.

I study invasive forest insects and work with the USDA to develop easier ways of raising emerald ash borers and other invasive insects in research laboratories. This work is critical for discovering and testing ways to better manage forest recovery and prevent future outbreaks. But while the emerald ash borer has spread uncontrollably in nature, producing a consistent laboratory supply of these insects is surprisingly challenging – and developing an effective biological control program requires a lot of target insects.

Researchers believe the emerald ash borer likely arrived in the U.S. on imported wood packaging material from Asia sometime in the 1990s. The insects lay eggs in the bark crevices of ash trees; when larva hatch, they tunnel through the bark and feed on the inner layer of the tree. Their impact becomes apparent when the bark is peeled back, revealing dramatic feeding tracks. These channels damage the trees' vascular tissue – internal networks that transport water and nutrients – and ultimately kill the tree.

Before this invasive pest appeared on the scene, ash trees were particularly popular for residential developments, representing 20-40% of planted trees in some Midwestern communities. Emerald ash borers have killed tens of millions of U.S. trees with an estimated replacement cost of US$10-25 billion.

Ash wood is also popular for lumber used in furniture, sports equipment and paper, among many other products. The ash timber industry produces over 100 million board feet annually, valued at over $25 billion.

Why quarantines have failed

State and federal agencies have used quarantines to combat the spread of several invasive forest insects, including Asian longhorned beetles and *Lymantria dispar*, previously known as gypsy moth. This approach seeks to reduce the movement of eggs

and young insects hidden in lumber, nursery plants and other wood products. In counties where an invasive species is detected, regulations typically require wood products to be heat-treated, stripped of bark, fumigated or chipped before they can be moved.

The federal emerald ash borer quarantine started with 13 counties in Michigan in 2003 and increased exponentially over time to cover than a quarter of the continental U.S. Quarantines can be effective when forest insect pests mainly spread through movement of their eggs, hitchhiking long distances when humans transport wood.

However, female emerald ash borers can fly up to 12 miles per day for as long as six weeks after mating. The beetles also are difficult to trap, and typically are not detected until they have been present for three to five years – too late for quarantines to work.

Next option: Wasps

Any biocontrol plan poses concerns about unintended consequences. One notorious example is the introduction of cane toads in Australia in the 1930s to reduce beetles on sugarcane farms. The toads didn't eat the beetles, but they spread rapidly and ate lots of other species. And their toxins killed predators.

Introducing species for biocontrol is strictly regulated in the U.S. It can take two to 10 years to demonstrate the effectiveness of potential biocontrol agents, and obtaining a permit for field testing can take two more years. Scientists must demonstrate that the released species specializes on the target pest and has minimal impacts on other species.

Four wasp species from China and Russia that are natural enemies of the emerald ash borer have gone through the approval process for field release. These wasps are parasitoids: They deposit their eggs or larva into or on another insect, which becomes an unsuspecting food source for the growing parasite. Parasitoids are great candidates for biocontrol because they typically exploit a single host species.

The selected wasps are tiny and don't sting, but their egg-laying organs can penetrate ash tree bark. And they have specialized sensory abilities to find emerald ash borer larva or eggs to serve as their hosts.

An emerald ash borer larva in wood (left); Tetrastichus planipennisi, a parasitic wasp that preys on ash borers; and wasp larva that have grown and eaten the ash borer. **USDA, CC BY-ND**

The USDA is working to rear massive numbers of parasitoid wasps in lab facilities by providing lab-grown emerald ash borers as hosts for their eggs. Despite COVID-19 disruptions, the agency produced over 550,000 parasitoids in 2020 and released them at over 240 sites.

The goal is to create self-sustaining field populations of parasitoids that reduce emerald ash borer populations in nature enough to allow replanted ash trees to grow and thrive. Several studies have shown encouraging early results, but securing a future for ash trees will require more time and research.

One hurdle is that emerald ash borers grown in the lab need fresh ash logs and leaves to complete their life cycle. I'm part of a team working to develop an alternative to the time- and cost-intensive process of collecting logs: an artificial diet that the beetle larva can eat in the lab.

The food must provide the right texture and nutrition. Other leaf-feeding insects readily eat artificial diets made from wheat germ, but species whose larva digest wood are pickier. In the wild, emerald ash borers only feed on species of ash tree.

In today's global economy, with people and products moving rapidly around the world, it can be hard to find effective management options when invasive species become established over a large area. But lessons learned from the emerald ash borer

will help researchers mobilize quickly when the next forest pest arrives.

*Associate Professor of Biology, University of Richmond

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Partners

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Gelatins may protect the brain against Alzheimer's disease

A traditional Chinese medicine successfully protected neurons from amyloid-induced death

Kareem Clark

Grandma might have the right idea when bringing Jell-O salad to every church potluck.

Gelatins are animal-derived protein fragments created by breaking down collagen — a protein found in connective tissues like skin and ligaments.

Gelatins are also widely used medicinally, from skincare to joint pain. But traditional Chinese medicine also claims that they protect the brain against deteriorating diseases such as Alzheimer's disease. And a recent study published in Frontiers in Pharmacology put this historically anecdotal remedy to the test.

Researchers first mimicked Alzheimer's disease in a dish by treating lab-grown cells with a toxic protein fragment that accumulates in patient brain cells, called amyloid-beta. And like human Alzheimer's disease, amyloid-beta treatment induced profound cell death in this model. But, surprisingly, gelatin treatment completely protected these brain-like cells from this toxicity.

To understand how gelatins are neuroprotective, they turned to mitochondria — the powerhouses of the cell. Mitochondria are cellular structures that generate energy in the form of a molecule called ATP. Because healthy cells need ATP to function, mitochondrial dysfunction is harmful to cell survival and the primary cause of brain cell death in Alzheimer's disease.

The researchers, therefore, hypothesized that gelatins prevent amyloid-beta-induced cell death through mitochondrial protection. Indeed, the gelatin-treated mitochondria showed reduced structural damage, improved ATP production, and lower oxidative stress. Furthermore, they believe gelatins exert these protective effects by blocking excessive calcium from entering the cell, which can trigger mitochondrial damage, oxidative stress, and ultimately cell death.

Of course, while these results are exciting, the human brain is a little more complex than a dish of cells, and more work is necessary to determine the therapeutic potential of gelatins in human disease.

https://bit.ly/38nWCZt

Why Do Short Lung Infections Lead to Long-Lasting Lung Damage?

Study points to mechanism of post-viral lung damage; suggests targets of intervention.

The deadliest time in a viral respiratory illness sometimes is actually after the virus is cleared from the body. Destructive processes that are set in motion during an infection crest in the weeks after the virus is defeated, leading to organ damage that can cause chronic illness or even death. After an initial bout of COVID-19, for example, some people struggle with persistent cough, difficulty breathing and shortness of breath — signs of ongoing lung disease.

Researchers at Washington University School of Medicine in St. Louis have found clues to just how lung damage develops in the aftermath of a respiratory infection. Studying mice, they found that

infection triggers the expression of a protein called IL-33, which is needed for stem cells in the lung to overgrow into air spaces, and increases mucus production and inflammation in the lung. The findings, published on August 24, 2021, in the *Journal of Clinical Investigation*, reveal potential points of intervention to prevent chronic lung damage caused by viral infections.

"Vaccines, antivirals, antibody therapies are all helpful, but they are not a solution for people who are already on the road to progressive disease," said senior author Michael J. Holtzman, MD, the Selma and Herman Seldin Professor of Medicine and a professor of cell biology & physiology. "We've gotten better at taking care of the acute illness due to COVID-19, but what happens after that initial injury phase is still a major obstacle to a better outcome. At this point, we are also faced with tens of millions of people who already had infection, and a high percentage of them are having long-term disease, especially with respiratory symptoms. We don't have a treatment that can correct the problem."

It's long been recognized that acute respiratory infections can lead to chronic lung disease. Children hospitalized with respiratory syncytial virus, for example, are two to four times more likely to develop asthma that persists for long periods, maybe even for a lifetime. How exactly an acute respiratory infection triggers chronic disease, however, is not fully understood, making it difficult to develop therapies to prevent or treat it.

As part of this study, Holtzman and colleagues, including first author Kangyun Wu, PhD, an instructor in medicine, studied mice infected with Sendai virus. Sendai doesn't cause serious disease in people, but it naturally infects other animals including mice and causes respiratory infections that develop much like respiratory infections in people.

The researchers examined lung tissues from mice 12 and 21 days after infection with Sendai virus, and compared the samples to lung tissues of uninfected mice. They found that two populations of stem cells help maintain the barrier between the lung and the outside world in uninfected mice. After infection with Sendai virus, however, these two populations separately begin to multiply and spread into air spaces. Basal cells take over small airways and air sacs while AT2 cells remain confined to air sacs. Some of the new basal cells become mucus-producing cells while others release molecules that recruit immune cells to the lungs. Altogether, the process results in lungs with less air space, more mucus and ongoing inflammation that together interfere with breathing.

Further experiments showed that this process hinges on the protein IL-33. Under normal conditions, IL-33 increases in the nuclei of lung stem cells in response to stress or injury and helps the lung repair damaged barriers. During and after infection, though, IL-33 can take on a more detrimental role.

To assess the role of IL-33 in post-viral lung damage, the researchers genetically modified mice to lack IL-33 in the basal set of lung stem cells. The scientists then infected those mice — and a separate group of unmodified mice — with Sendai virus. The two groups of mice were equally effective at fighting off an initial Sendai virus infection. But three weeks after infection, the lungs of the mice that lacked IL-33 exhibited less cellular overgrowth, mucus and inflammation, indicating that they had fewer signs of harmful lung changes. At seven weeks after infection, the mice without IL-33 in basal cells also had higher oxygen levels in their blood and less airway hyperresponsiveness, both of which are signs of improvement in their chronic lung disease.

"These results were really nice to see because getting rid of IL-33 and in turn losing basal stem cells could have made things worse," Holtzman said. "The engineered mice could have died because they were no longer able to perform the normal repair of the viral damage to the lung barrier. But that's not the case. The mice

lacking this population of basal cells instead had much better outcomes. That's what we're excited about. These findings put us on firm ground to find therapies that correct the bad behavior of basal stem cells."

Targeting steps on the pathway between IL-33 and basal cell activation could form the basis of broadly effective therapies to prevent or treat lung disease caused by a variety of viruses and perhaps other forms of injury in the lung and other sites where the body meets the outside world, Holtzman said.

"The lung has a pretty stereotyped response to injury, including viral injury," Holtzman said. "The specific type of virus, the genetics of the host, the severity of the initial illness — all of these things influence the outcome, but they're just matters of degrees. You still see the same key elements across conditions, and that's why we believe that there can be a common strategy for treatment. We have a drug discovery program to find such a common strategy, and this study fits well with that."

Reference: "Basal-epithelial stem cells cross an alarmin checkpoint for post-viral lung disease" by Kangyun Wu, Kenji Kamimoto, Yong Zhang, Kuangying Yang, Shamus P. Keeler, Benjamin J. Gerovac, Eugene V. Agapov, Stephen P. Austin, Jennifer Yantis, Kelly A. Gissy, Derek E. Byers, Jennifer Alexander-Brett, Christy M. Hoffmann, Matthew Wallace, Michael E. Hughes, Erika C. Crouch, Samantha A. Morris and Michael J. Holtzman, 24 August 2021, Journal of Clinical Investigation.

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https://bit.ly/3BpfZ0M

400-Million-Year-Old Fossils Reveal How the First Roots Evolved

A plant fossil from a geological formation in Scotland sheds light on the development of the earliest known form of roots.

A team led by researchers at GMI – the Gregor Mendel Institute of Molecular Plant Biology of the Austrian Academy of Sciences, the University of Edinburgh, and the University of Oxford realize the first 3D reconstruction of a Devonian plant based exclusively on fossil evidence. The findings demonstrate that the appearance of different axis types at branching points resulted in the evolution complexity soon after land plants evolved sometime before 400 million years ago. The results are published in *eLife*.

New research demonstrates how the oldest known root axed developed more than 400 million years ago. The evolution of roots at this time was a dramatic event that impacted our planet and atmosphere and resulted in transformative ecological and climate change.

Artist's reconstruction of what Asteroxylon mackiei would have looked like in life. Each leafy shoot is roughly 1 cm in diameter. **Credit: Matt Humpage**

The first evidence-based 3D reconstruction of the fossil *Asteroxylon mackiei*, the most structurally complex plant from the Rhynie chert has shown how roots and other types of axes developed in this ancient plant. The fossil is preserved in chert (a type of flint) found near village of Rhynie in Aberdeenshire, Scotland. The specimens are exceptionally well-preserved in the 407-million-year-old rocks from the Early Devonian period.

The extinct genus *Asteroxylon* belongs to the group of plants called the lycophytes, a class that also comprises living representatives such as isoetes and selaginella. The reconstruction has allowed researchers, for the first time, to glean both anatomical and developmental information of this mysterious fossil. This is of particular significance because previous interpretations of the structure of this fossil plant were based to a large extent on comparisons of fragmentary images with extant plants.

The reconstruction demonstrates that these plants developed roots in an entirely different way than extant plants develop roots today. The rooting axes of *A. mackiei* are the earliest known types of plant

roots.

"These are the oldest known structures that resemble modern roots and now we know how they formed. They developed when a shoot-like axis formed a fork where one prong maintained its shoot identity and the second developed root identity," says Dolan. This mechanism of branching, called "dichotomous branching," is known in living plants within tissues that share structural identity. However, as Dolan stresses: "No roots develop in this way in living plants, demonstrating that this mechanism of root formation is now extinct." Their findings demonstrate how a now extinct rooting system developed during the evolution of the first complex land plant.

"100 Years after the discovery of the fossils in Rhynie, our reconstruction demonstrates what these enigmatic plants really looked like! The reconstruction also demonstrates how the roots formed" exclaims GMI group leader Liam Dolan, co-corresponding author on the work. Understanding the structure and evolution of these plants from the Early Devonian period provides us with an insight into events at a key time in Earth history just after plants colonized the dry surfaces of the continents as they began to spread – radiate – across the land.

"Their evolution, radiation, and spread across all continents had a dramatic impact on the Earth system. Plant roots reduced atmospheric CO_2 levels, stabilized the soil and revolutionized water circulation across the surfaces of continents," states first author and co-corresponding author Alexander (Sandy) J. Hetherington, group leader at the University of Edinburgh. At the root of the environmental and ecological impact of plant evolution are the plant roots themselves!

Hetherington highlighted how his research was enabled by fossils that were collected by generations of paleontologists that are housed in many different museums and universities. "The answers to so many of the key questions of evolution are lying in shelves in these institutions" said the scientist who is now based at the University of Edinburgh. "Using digital 3D techniques it is possible for the first time to visualize the complex body plan of *A. mackiei* allowing us to discover how these enigmatic plants developed. It was brilliant to finally see details that had previously been hidden."

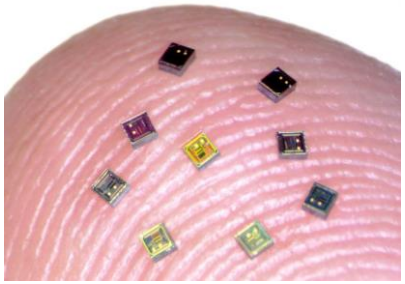
Reference: "An evidence-based 3D reconstruction of Asteroxylon mackiei, the most complex plant preserved from the Rhynie chert" by Alexander J Hetherington, Siobhán L Bridson, Anna Lee Jones, Hagen Hass, Hans Kerp and Liam Dolan, 24 August 2021, eLife.
DOI: 10.7554/eLife.69447

https://bit.ly/3tajQMp

Wireless Microscale Neural Sensors Enable Next-Generation Brain-Computer Interface System

Coordinated network of independent, wireless microscale neural sensors, each about the size of a grain of salt, to record and stimulate brain activity

Brain-computer interfaces (BCIs) are emerging assistive devices that may one day help people with brain or spinal injuries to move or communicate. BCI systems depend on implantable sensors that record electrical signals in the brain and use those signals to drive external devices like computers or robotic prosthetics.



Tiny chips called neurograins are able to sense electrical activity in the brain and transmit that data wirelessly. **Credit: Jihun Lee / Brown University**

Most current BCI systems use one or two sensors to sample up to a few hundred neurons, but neuroscientists are interested in systems that are able to gather data from much larger groups of brain cells.

Now, a team of researchers has taken a key step toward a new concept for a future BCI system — one that employs a coordinated network of independent, wireless microscale neural sensors, each about the size of a grain of salt, to record and stimulate brain

activity. The sensors, dubbed "neurograins," independently record the electrical pulses made by firing neurons and send the signals wirelessly to a central hub, which coordinates and processes the signals.

In a study published on August 12, 2021, in *Nature Electronics*, the research team demonstrated the use of nearly 50 such autonomous neurograins to record neural activity in a rodent.

The results, the researchers say, are a step toward a system that could one day enable the recording of brain signals in unprecedented detail, leading to new insights into how the brain works and new therapies for people with brain or spinal injuries.

"One of the big challenges in the field of brain-computer interfaces is engineering ways of probing as many points in the brain as possible," said Arto Nurmikko, a professor in Brown's School of Engineering and the study's senior author. "Up to now, most BCIs have been monolithic devices — a bit like little beds of needles. Our team's idea was to break up that monolith into tiny sensors that could be distributed across the cerebral cortex. That's what we've been able to demonstrate here."

The team, which includes experts from Brown, Baylor University, University of California at San Diego and Qualcomm, began the work of developing the system about four years ago. The challenge was two-fold, said Nurmikko, who is affiliated with Brown's Carney Institute for Brain Science. The first part required shrinking the complex electronics involved in detecting, amplifying and transmitting neural signals into the tiny silicon neurograin chips. The team first designed and simulated the electronics on a computer, and went through several fabrication iterations to develop operational chips.

The second challenge was developing the body-external communications hub that receives signals from those tiny chips. The device is a thin patch, about the size of a thumb print, that attaches to the scalp outside the skull. It works like a miniature cellular phone tower, employing a network protocol to coordinate the signals from the neurograins, each of which has its own network address. The patch also supplies power wirelessly to the neurograins, which are designed to operate using a minimal amount of electricity.

"This work was a true multidisciplinary challenge," said Jihun Lee, a postdoctoral researcher at Brown and the study's lead author. "We had to bring together expertise in electromagnetics, radio frequency communication, circuit design, fabrication and neuroscience to design and operate the neurograin system."

The goal of this new study was to demonstrate that the system could record neural signals from a living brain — in this case, the brain of a rodent. The team placed 48 neurograins on the animal's cerebral cortex, the outer layer of the brain, and successfully recorded characteristic neural signals associated with spontaneous brain activity.

The team also tested the devices' ability to stimulate the brain as well as record from it. Stimulation is done with tiny electrical pulses that can activate neural activity. The stimulation is driven by the same hub that coordinates neural recording and could one day restore brain function lost to illness or injury, researchers hope.

The size of the animal's brain limited the team to 48 neurograins for this study, but the data suggest that the current configuration of the system could support up to 770. Ultimately, the team envisions scaling up to many thousands of neurograins, which would provide a currently unattainable picture of brain activity.

"It was a challenging endeavor, as the system demands simultaneous wireless power transfer and networking at the mega-bit-per-second rate, and this has to be accomplished under extremely tight silicon area and power constraints," said Vincent Leung, an associate professor in the Department of Electrical and

Computer Engineering at Baylor. “Our team pushed the envelope for distributed neural implants.”

There’s much more work to be done to make that complete system a reality, but researchers said this study represents a key step in that direction.

“Our hope is that we can ultimately develop a system that provides new scientific insights into the brain and new therapies that can help people affected by devastating injuries,” Nurmikko said.

Reference: “Neural recording and stimulation using wireless networks of microimplants” by Jihun Lee, Vincent Leung, Ah-Hyoung Lee, Jiannan Huang, Peter Asbeck, Patrick P. Mercier, Stephen Shellhammer, Lawrence Larson, Farah Laiwalla and Arto Nurmikko, 12 August 2021, Nature Electronics.

DOI: 10.1038/s41928-021-00631-8

Other co-authors on the research were Ah-Hyoung Lee (Brown), Jiannan Huang (UCSD), Peter Asbeck (UCSD), Patrick P. Mercier (UCSD), Stephen Shellhammer (Qualcomm), Lawrence Larson (Brown) and Farah Laiwalla (Brown). The research was supported by the Defense Advanced Research Projects Agency (N66001-17-C-4013).