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Researchers find a way to mend a broken heart

A Monash University study has uncovered for the first time a way to prevent and reverse damage caused by broken-heart syndrome, also known as Takotsubo cardiomyopathy.

Using mouse models, the pre-clinical study published in the acclaimed journal *Signal Transduction and Targeted Therapy*, has shown the cardioprotective benefit of a drug called Suberanilohydroxamic acid, or SAHA, dramatically improved cardiac health and reversed the broken-heart. The landmark study used SAHA to target genes and is a world first for Takotsubo cardiomyopathy.

SAHA, currently used for cancer treatment, is approved by the US Food and Drug Administration (FDA) and Australian Therapeutic Goods Administration (TGA), works by providing a protective benefit to genes and in particular the acetylation/deacetylation (Ac/Dc) index, an important process that regulates gene expression.

The goal of the study, led by Professor Sam El-Osta from Monash Central Clinical School, was to better understand the regulatory mechanism as a first step towards improved treatment plans.

"We show for the first time a drug that shows preventative and therapeutic benefit is important to a healthy heart. The drug not only slows cardiac injury, but also reverses, the damage caused to the stressed heart," Professor El-Osta said.

Broken-heart syndrome is a weakening of the left ventricle, the heart's main pumping chamber and is brought on by stressful emotional triggers often following traumatic events such as the death of a loved one or a family separation. This condition mimics a heart attack with chest pain, shortness of breath and irregular heartbeat.

In western countries there is a clear, uneven distribution among patients with Takotsubo - the condition occurs almost exclusively in women, especially after menopause, with new research suggesting that up to 8 per cent of women suspected of having a heart attack may have this disorder.

While the main symptoms are chest pain and shortness of breath, the precise cause isn't known. Experts think that surging stress hormones essentially flood the heart, triggering changes in heart muscle cells or coronary blood vessels (or both) that prevent the left ventricle from contracting effectively. This causes the heavy-achy-feeling you get in the chest which can be mistaken as a heart attack.

Most patients recover fully within two months which is the good news, but the bad news is that along the way some patients suffer from significant heart failure and other in-hospital complications. There is no standard treatment for broken-heart and while death is rare, heart failure occurs in about 20 per cent of patients, with therapeutic options remaining limited.

"This pre-clinical study describes a new standard in preventative and therapeutic potential using a cardioprotective drug that targets genes in the heart," Professor El-Osta said.

The team is committed to the research of women's health recognising the uneven sex prevalence of almost 9:1 (female to male). Based on these promising results we are focussed on the continued development of compounds like SAHA to improve cardiac benefit and healthier life."

Read the full paper published in Signal Transduction and Targeted Therapy titled: SAHA Attenuates Takosubo-like Myocardial Injury by Targeting an Epigenetic Ac/Dc Axis. DOI: 10.1038/s41392-021-00546-y

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Were the first humans superpredators?

Humans specialized in taking down gigantic prey more than 2 million years ago, according to the new hypothesis.

By Stephanie Pappas - Live Science Contributor

The first humans were mega-carnivores who took down prey with savvy hunting skills, a controversial new study suggests.

In a new research paper, scientists argue that humans and their close relatives were expert hunters from early on, starting at least 2 million years ago. Not only that, but the earliest human species were superpredators, taking down animals twice as large as any terrestrial creature alive today, said Miki Ben-Dor and Ran Barkai, researchers at Tel Aviv University in Israel, and Raphael Sirtoli, a doctoral student at the University of Minho in Portugal.

"So far, attempts to reconstruct the diet of Stone Age humans were mostly based on comparisons to 20th-century hunter-gatherer societies," Ben-Dor said in a statement. "This comparison is futile, however, because 2 million years ago, hunter-gatherer societies could hunt and consume elephants and other large animals — while today's hunter-gatherers do not have access to such bounty. The entire ecosystem has changed, and conditions cannot be compared."

Steppe Mammoths, one example of a megaherbivore that has gone extinct. This species likely went extinct around 200,000 years ago in Europe. **(Image credit: Beth Zaiken/Center for Palaeogenetics)**

A limited record

Fossil evidence from the earliest human ancestors is scarce. But based on archaeological evidence, Ben-Dor told Live Science, it's clear that *Homo sapiens* and their close relatives ate "anything edible." But how much of their diets comprised plants versus animals is the sticking point. (Another sticking point: When did humans start hunting meat themselves, rather than scavenging it?) Many animals considered omnivorous actually have diets weighted one way or another. Chimpanzees, for example, are technically omnivores, but meat makes up only about 6% of their diets, according to the Jane Goodall Institute of Canada. Dogs and wolves eat mostly meat but sometimes gorge on grains, leading to a debate over whether they should be classified as omnivores or carnivores.

The ancient human species *Homo habilis* was eating meat at least 2.6 million years ago, Ben-Dor said. Another early human species, *Homo erectus*, seems to have been a particularly enthusiastic meat eater by 1.8 million years ago; its teeth and gut shrank compared with earlier ancestors — adaptations for digesting meat instead of plants — and it used stone tools capable of butchering meat.

Ben-Dor and Barkai argue in their paper, published March 5 in the American Journal of Physical Anthropology, that meat wasn't just a bonus for these human species and the first *Homo sapiens*. Instead, the authors believe large animals weighing over 2,200 lbs. (1,000 kilograms) — such as elephants, hippopotamuses and rhinoceroses — made up most of humans' diets. These huge herbivores were much more common — and much larger — in the Pleistocene epoch, starting about 2.5 million years ago, than they are today. .

"Elephants 500,000 years ago could weigh 12 tons, compared to 4 to 6 tons today," Ben-Dor said.

These animals would have been walking buffets of fatty meat, well suited to feeding humans' energy-hungry brains, according to the researchers. The authors argued in another recent paper that hunting large prey might have been what drove human brain evolution.

This idea is controversial, however, and researchers do not agree on how useful a huge influx of meat would have been to hunter-gatherers in the days before refrigeration, nor on how skilled ancient humans would have been at taking down prey that other apex carnivores, like lions, struggle to defeat.

"There are some archaeologists who'd say, 'Yeah, they hunted elephant once in a while, but that was like a once-in-a-lifetime hunt; that's the thing grandparents would tell their kids stories about,'" said John Hawks, a paleoanthropologist at the University of Wisconsin-Madison who was not involved in the research. "There

are others who said 'No, meat from an elephant can last a long time. … Without storage, it's less than you think, but it was a regular part of their subsistence, and it was important to them.'"

A fatty diet?

Eating large, fatty animals would have been a benefit to the earliest humans, Ben-Dor and his colleagues wrote in their paper, because bringing down that many calories in one hunting trip — rather than multiple attempts to stalk smaller prey —— would have freed up time for other pursuits, such as toolmaking and child-rearing. The researchers argue that humans show adaptations for this high-fat, meat-heavy life, ranging from particularly acidic stomach juices (also found in other animals with meat-heavy diets) to small jaws (because meat eaters have to chew less than herbivores that must break down large amounts of fibrous vegetation for the same calories).

Archaeologically speaking, it's difficult to categorize humans and their relatives as one level of predator prior to about 50,000 years ago, Ben-Dor said. That's because the only reliable biochemical way to distinguish whether an animal is a top predator or fits lower on the food chain is a method called stable nitrogen isotope analysis, which requires testing collagen for molecules introduced into the body via the diet. Consumers contain a few percentage points more of the isotope nitrogen-15 than what is found in either the plants or animals they eat, making it possible to determine their level in the food web, also known as their trophic level.

Collagen, the connective tissue found in abundance in bones, doesn't preserve well prior to 50,000 years ago, though. The samples from that era hail from Europe, where cooler temperatures allow for better preservation, and they do indicate that humans were eating large mammals. However, 50,000 years ago in Europe is a far cry from 300,000 years ago in Africa, when and where the first *H. sapiens* arose, Hawks said.

Adding to the difficulties in determining ancient humans' diets, it's hard to determine precise dates for archaeological materials from the crucial time periods in the middle Pleistocene, when human diets were evolving, Hawks added.

"This is a time frame when our ability to determine the age of things relies on methods that have about a 100,000-year, sometimes 50,000-year, span of uncertainty about them. … That's a lot of error," Hawks told Live Science. And there are far fewer sites to make inferences from that are older than 100,000 years compared with those younger than 100,000 years, he said.

Despite the limited evidence from humanity's early evolution, the researchers said there is more work to be done to show whether these human ancestors truly were specialized carnivores. This might include more work on the abundance of animals of different sizes throughout the Pleistocene, explorations of genetic changes over time that would have altered humans' ability to digest different foods and comparisons of trends in prey size over time.

"I feel that we have only scratched the surface, exploring paleobiology's potential to discover our past and present adaptation to consuming meat and animal fat," Ben-Dor said.

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Supplement treats schizophrenia in mice, restores healthy "dance" and structure of neurons

Repurposed drug works by building cells' skeleton and transportation network

A simple dietary supplement reduces behavioral symptoms in mice with a genetic mutation that causes schizophrenia. After additional experiments, including visualizing the fluorescently stained dancing edge of immature brain cells, researchers concluded that the supplement likely protects proteins that build neurons' cellular skeletons.

The supplement betaine was first isolated from sugar beets and is

often associated with sweetness or umami flavor. Healthy levels of betaine come from both external food sources and internal synthesis in the body. Betaine supplements are already used clinically to treat the metabolic disease homocystinuria.

"I don't encourage anyone to take betaine for no reason, if a doctor has not recommended it. But, we know this drug is already used clinically, so repurposing it to treat schizophrenia should be safe," said Project Professor Nobutaka Hirokawa, M.D., Ph.D., from the University of Tokyo Graduate School of Medicine who led the recent research project. Hirokawa has been a member of the Japan Academy, a national honorary organization recognizing scientific achievement, since 2004 and received a Person of Cultural Merit award from the Japanese government in 2013.

Schizophrenia is estimated to affect about 1 in 100 people globally and is one of the top 15 leading causes of disability worldwide.

"There are treatments for schizophrenia, but they have side effects and unfortunately there is still no effective drug for patients to take that we can explain biochemically why it works," explained Hirokawa.

Genetic studies of people diagnosed with schizophrenia have found possible links between the disease and variations in the kinesin family 3b (kif3b) gene as well as another gene involved in the body's internal synthesis of betaine.

Hirokawa and his lab members have categorized all 45 members of the kinesin superfamily of genes in mammals, most of which encode motor proteins that move materials throughout the cell. Normally, the KIF3B protein links together with another kinesin superfamily protein and transports cargo throughout a neuron by traveling up and down the cell's skeleton.

Mice used in the recent research had only one functional copy of the kif3b gene and are often used as an animal model of schizophrenia. These mice avoid social interactions and show the same weak response as human patients with schizophrenia in a test called prepulse inhibition, which measures how startled they are by a sudden, loud sound preceded by a quieter sound.

Kif3b mutant mice raised on a diet supplemented with three times the normal amount of betaine had normal behavior, indicating that betaine supplements could treat schizophrenia symptoms.

To figure out why betaine had this effect on mice, researchers grew nerve cells with the kif3b mutation in the laboratory and added fluorescent labels so they could watch the cellular skeleton take shape.

The shape of a healthy neuron is reminiscent of a tree: a cell body surrounded by branches, the dendrites, attached to a long trunk, the axon. Kif3b mutant neurons grown in the lab have an unusual, hyperbranched structure with too many dendrites. Similar hyperbranched neurons are also seen in brain samples donated by people with schizophrenia, regardless of what treatments or medications they took while they were alive.

During healthy neuron development, the main body of the cell fills with a skeleton component called tubulin. Meanwhile, the front growth cone of the cell builds outwards in a spiky, erratic dance due to the movements of another skeleton component called filamentous actin. In kif3b mutants, this dancing movement, which experts refer to as lamellipodial dynamics, is noticeably reduced and the division between tubulin and actin is blurred.

The actin in a neuron's cellular skeleton is assembled in part by another protein called CRMP2. Chemical analyses of the brains of kif3b mutant mice and human schizophrenia patients reveal significant chemical damage to CRMP2, which causes the proteins to clump together.

Betaine is known to prevent the type of chemical damage, carbonyl stress, that causes this CRMP2 dysfunction.

"In postmortem brains of schizophrenia patients, CRMP2 is the

protein in the brain with the most carbonyl stress. Betaine likely eliminates the carbonyl stress portion of the schizophrenia equation," said Hirokawa.

By protecting CRMP2 from damage, betaine treatment allows kif3b mutant neurons to build proper structures. With a structurally sound skeleton to navigate, the remaining functional KIF3B protein can shuttle cargo around the cell. Other test tube experiments revealed that KIF3B and CRMP2 can bind together, but their exact relationship remains unclear.

"We know that the amount of betaine decreases in schizophrenia patients' brains, so this study strongly suggests betaine could be therapeutic for at least some kinds of schizophrenia," said Hirokawa.

The UTokyo research team is planning future collaborations with pharmaceutical companies and clinical studies of betaine supplements as a treatment for schizophrenia.

This research is a peer-reviewed experimental study in mice and human cells published in the journal Cell Reports.

Research Publication

Shogo Yoshihara, Xuguang Jiang, Momo Morikawa, Tadayuki Ogawa, Sotaro Ichinose, Hirooki Yabe, Akiyoshi Kakita, Manabu Toyoshima, Yasuto Kunii, Takeo Yoshikawa, Yosuke Tanaka, Nobutaka Hirokawa. 13 April 2021. Betaine ameliorates schizophrenic traits by functionally compensating for KIF3-based CRMP2 transport. Cell Reports. DOI: 10.1016/j.celrep.2021.108971 https://doi.org/10.1016/j.celrep.2021.108971

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New COVID-19 vaccine may offer broad protection from coronaviruses

Costs about $1 a dose and has shown promising results

A COVID-19 vaccine that could provide protection against existing and future strains of the COVID-19 coronavirus, and other coronaviruses, and cost about $1 a dose has shown promising results in early animal testing.

Vaccines created by UVA Health's Steven L. Zeichner, MD, PhD, and Virginia Tech's Xiang-Jin Meng, MD, PhD, prevented pigs from being becoming ill with a pig model coronavirus, porcine epidemic diarrhea virus (PEDV). The vaccine was developed using an innovative approach that Zeichner says might one day open the door to a universal vaccine for coronaviruses, including coronaviruses that previously threatened pandemics or perhaps even coronaviruses that cause some cases of the common cold.

Their coronavirus vaccine offers several advantages that could overcome major obstacles to global vaccination efforts. It would be easy to store and transport, even in remote areas of the world, and could be produced in mass quantities using existing vaccine-manufacturing factories.

The UVA and Virginia Tech scientists created the vaccine using a new platform Zeichner invented to rapidly develop new vaccines. So the testing success bodes well for both the COVID-19 vaccine and Zeichner's vaccine-development approach.

"Our new platform offers a new route to rapidly produce vaccines at very low cost that can be manufactured in existing facilities around the world, which should be particularly helpful for pandemic response," Zeichner said.

New Vaccine Approach

Zeichner's new vaccine-production platform involves synthesizing DNA that directs the production of a piece of the virus that can instruct the immune system how to mount a protective immune response against the virus.

That DNA is inserted into another small circle of DNA called a plasmid that can reproduce within bacteria. The plasmid is then introduced into bacteria, instructing the bacteria to place pieces of proteins on their surfaces. The technique uses the common bacteria E. coli.

One major innovation is that the E. coli have had a large number of its genes deleted. Removing many of the bacteria's genes, including genes that make up part of its exterior surface or outer membrane, appears to substantially increase the ability of the immune system

to recognize and respond to the vaccine antigen placed on the surface of the bacteria.

To produce the vaccine, the bacteria expressing the vaccine antigen are simply grown in a fermenter, much like the fermenters used in common microbial industrial processes like brewing, and then killed with a low concentration of formalin.

"Killed whole-cell vaccines are currently in widespread use to protect against deadly diseases like cholera and pertussis. Factories in many low-to-middle-income countries around the world are making hundreds of millions of doses of those vaccines per year now, for a $1 per dose or less," Zeichner said. "It may be possible to adapt those factories to make this new vaccine. Since the technology is very similar, the cost should be similar too."

The entire process, from identifying a potential vaccine target to producing the gene-deleted bacteria that have the vaccine antigens on their surfaces, can take place very quickly, in only two to three weeks, making the platform ideal for responding to a pandemic.

Targeting Coronavirus

Zeichner and Meng's vaccine takes an unusual approach in that it targets a part of the spike protein of the virus, the "viral fusion peptide," that is essentially universal among coronaviruses. The fusion peptide has not been observed to differ at all in the many genetic sequences of SARS-CoV-2, the virus that causes COVID-19, that have been obtained from thousands of patients around the world during the pandemic.

Meng and Zeichner made two vaccines, one designed to protect against COVID-19, and another designed to protect against PEDV. PEDV and the virus that causes COVID-19 are both coronaviruses, but they are distant relatives. PEDV and SARS-CoV-2, like all coronaviruses, share several of the amino acids that constitute the fusion peptide. PEDV infects pigs, causing diarrhea, vomiting and high fever, and has been a large burden on pig farmers around the world. When PEDV first appeared in pig herds in the US, it killed almost 10% of US pigs - a pig pandemic.

One advantage of studying PEDV in pigs is that Meng and Zeichner could study the ability of the vaccines to offer protection against a coronavirus infection in its native host - in this case, pigs. The other models that have been used to test COVID-19 vaccines study SARS-CoV-2 in non-native hosts, such as monkeys or hamsters, or in mice that have been genetically engineered to enable them to be infected with SARS-CoV-2. Pigs are also very similar in physiology and immunology to people - they may be the closest animal models to people other than primates.

In some unexpected results, Meng and Zeichner observed that both the vaccine against PEDV and the vaccine against SARS-CoV-2 protected the pigs against illness caused by PEDV. The vaccines did not prevent infection, but they protected the pigs from developing severe symptoms, much like the observations made when primates were tested with candidate COVID-19 vaccines. The vaccines also primed the immune system of the pigs to mount a much more vigorous immune response to the infection. If both the PEDV and the COVID-19 vaccines protected the pigs against disease caused by PEDV and primed the immune system to fight the disease, it is reasonable to think that the COVID-19 vaccine would also protect people against severe COVID-19 disease, the scientists say.

Next Steps

Additional testing - including human trials - would be required before the COVID-19 vaccine could be approved by the federal Food and Drug Administration or other regulatory agencies around the world for use in people, but the collaborators are pleased by the early successes of the vaccine-development platform.

Zeichner added that he was encouraged that a collaboration between UVA and Virginia Tech, schools with a well-known sports

rivalry, has produced such promising results.

"XJ is just an amazing collaborator and a wonderful scientist. And he is incredibly generous with his time and the resources he has available," Zeichner said. "If UVA and Virginia Tech scientists can work together to try to do something positive to address the pandemic, then maybe there is some hope for collaboration and cooperation in the country at large."

About the Research

The researchers have published their findings in the scientific journal PNAS. The findings are under peer review. The research team consisted of Denicar Lina Nascimento Fabris Maeda, Debin Tian, Hanna Yu, Nakul Dar, Vignesh Rajasekaran, Sarah Meng, Hassan Mahsoub, Harini Sooryanarain, Bo Wang, C. Lynn Heffron, Anna Hassebroek, Tanya LeRoith, Xiang-Jin Meng and Steven L. Zeichner.

Zeichner is the McClemore Birdsong Professor in the Departments of Pediatrics and Microbiology, Immunology and Cancer Biology, the director of the Pendleton Pediatric Infectious Disease Laboratory and part of UVA Children's Child Health Research Center. Meng is University Distinguished Professor, and a member of Virginia Tech's Department of Biomedical Sciences & Pathobiology.

Their vaccine-development work was supported by the Pendleton Pediatric Infectious Disease Laboratory, the McClemore Birdsong endowed chair and by generous support from the University of Virginia Manning Fund for COVID-19 Research and from the Ivy Foundation. The work was also partially supported by the Virginia-Maryland College of Veterinary Medicine (FRS#175420), and Virginia Tech internal funds (FRS#440783).

https://wb.md/3dJmPoJ

Next-Generation COVID Vaccines Have Many Different Targets

Vaccine developers are monitoring the durability of the immune response of current COVID vaccines while racing against variants to provide more options for protection, no matter what happens next in the pandemic.

Emily Willingham

Vaccine research, which used to be on the back burner, making only slow progress, has been fast-tracked in the past year, pushing the field of vaccinology forward, says Deborah Fuller, PhD, professor of microbiology and vaccine developer at the University of Washington School of Medicine in Seattle.

The emergence of dozens of vaccine candidates in less than a year has been nothing short of extraordinary, and "we're going to have an amazing toolbox to use to combat infectious disease for a long time to come," she says.

Booster shots are part of the plan to protect against COVID-19, but so are entirely new approaches to vaccines, including delivery routes that eliminate the need for injections, and easier storage to help ease vaccine supply shortages.

Supply-chain problems are the first major obstacles that teams like Fuller's are tackling. Anything that can break vaccines free of the so-called cold chain — the need for deep freezing or refrigeration — is a priority, she explains. The ability to store vaccines at room temperature would increase accessibility in parts of the world where cold storage is hard to come by.

We're going to have an amazing toolbox to use to combat infectious disease for a long time to come.

The messenger (m)RNA vaccines, like the Pfizer and Moderna ones currently being used in the United States, are the most temperature-sensitive. "You can just look at a global map of where they're distributed and see which countries can accommodate the cold chain," says Fuller. Companies that produce the mRNA vaccines are working on different formulations to make the molecules stable at room temperature, she explains.

The vaccines that rely on viral vectors, such as those produced by Johnson & Johnson and AstraZeneca, "are stored at much nicer temperatures," says Anna Blakney, PhD, a vaccine developer and assistant professor in the Michael Smith Laboratories and the School of Biomedical Engineering, University of British Columbia, in Vancouver, Canada. Improvements in storage requirements across the board "will be here before we know it."

People who have received either of the two-shot mRNA vaccines might already be familiar with the common adverse effects of

fatigue, arm pain, fever, aches, and chills, which are directly related to the mRNA in the vaccine, explains Blakney. "Being able to optimize the dose will cut down on side effects and presumably have the same efficacy."

Reducing Adverse Effects

The self-amplifying mRNA vaccines currently in development contain a lot of antigens to stimulate a strong immune response but have fewer infected cells. With less mRNA but an added replication protein, the molecule can make more copies of itself once it is inside the cell, with fewer adverse effects, says Blakney.

And with a strong immune response, a booster might not even be needed, Fuller adds.

As vaccination becomes more common and the threat of COVID-related death diminishes, one of the next priorities will be to minimize adverse effects. With an endemic virus circulating at low levels, "you're probably not willing to lose a day or two of work to suffer side effects," says Gregory Poland, MD, director of the Mayo Vaccine Research Group in Rochester, Minnesota.

And people might be able to avoid the needle entirely if some next-generation candidates get off the ground. At least seven non-injectable vaccines are in development, including a version of AstraZeneca's ChAdOx1 nCoV-19 (AZD1222).

Vaccines that could be delivered directly to the nose, for example, might confer mucosal protection, according to Fuller. Nasal vaccines don't have to be administered by a trained clinician and have the added advantage of inducing antibodies in the respiratory system to stop the virus before it gets a cellular foothold, she explains.

No Needles

Other groups are developing "swish-and-swallow" and pill-based vaccines, Poland reports. "The beauty of this touches on the self-administered option," says Fuller. Imagine if people could have picked up self-administered vaccines in pharmacies early on in the pandemic. "We would have shut this thing down by now."

But despite the fast pace of COVID vaccine development, ongoing struggles in vaccine research programs remain and will likely create obstacles in coronavirus vaccine research. A pan-virus vaccine — a "brass ring" in vaccine development — has been elusive for many infectious diseases, including influenza and HIV.

Some vaccinologists are trying to develop a meta-pan-virus vaccine that covers both influenza and coronaviruses, which would enable a single immunization to protect against both viruses, says Poland, who is working on vaccines for COVID-19.

Universal Vaccines

The high rates of morbidity, death, and long-term symptoms related to COVID-19 have pushed the search for a pan-coronavirus vaccine into high gear.

At the onset of the pandemic, "the house was on fire" so developers focused on the most expedient way to get vaccines out, says Poland. A focus on spike sequences from already circulating strains of COVID-19 was the fastest, most efficient approach.

Now researchers have time to look at pan-coronavirus candidates, and will rely on these narrow-target vaccines that can be updated to take on emerging variants. The tricky part about pan-coronavirus vaccines, Fuller explains, is that they are "not something we're looking at next year, but probably a good 5 years down the line."

Even more difficult, she adds, is the identification of a part of the virus that won't mutate much but will still trigger an immune response. "The parts that are really vulnerable are poorly immunogenic, and the immune system can't 'see' them," so getting around this problem is "not trivial."

But the pace of vaccine development has accelerated during the pandemic and a first workable pan-virus vaccine is in sight.

A peptide-based version of a vaccine that targets several

coronavirus antigens is being developed by Poland's team. And researchers are already testing a multivalent two-dose candidate at the Walter Reed Army Institute of Research. Their platform will allow add-ons of antigens from other coronaviruses to protect broadly and proactively against multiple coronavirus species and strains.

Researchers are also investigating the use of different combinations of vaccines to bolster an immune response with a cocktail of antigens. A trial of sequential immunization with Pfizer's mRNA-based vaccine and AstraZeneca's adenovirus-vectored version is underway in the United Kingdom. For mRNA vaccines, a cocktail could be built with multiple mRNA sequences that encode different bits of the virus, Blakney explains.

But how much protection is needed? "We don't know if there are certain thresholds of antibodies" that would be a marker of sufficient protection, she says. This is a strategy used for polio vaccines, and some clinical trial data already suggest that a target antibody level could be identified, she points out.

This threshold could also guide decision-making about boosters. "We don't know what level we need to meet, and the second dose increases your immunity so much," says Blakney. "There is a possibility that you'd only need one if you got to that antibody level" determined to be protective. "That would open up a lot of doors."

https://bit.ly/3nhto4W

Forgotten species could future-proof coffee in a warming world

Almost all the world's coffee is from just two species—Arabica and Robusta

by Kelly MacNamara

A once-prized coffee species, rediscovered in West Africa decades after it was thought to have disappeared, is just as tasty as high-end Arabica and more resilient to climate change, scientists said Monday, adding that the forgotten bean could help future-proof quality coffee.

While there are more than a hundred known coffee species, the world gets its caffeine hit mostly from the beans of just two—Arabica, considered to be the superior brew, and the less refined Robusta, mostly used for instant mixes.

But climate change presents a serious challenge for the multi-billion dollar coffee industry and the roughly 100 million farmers worldwide who earn a living from cultivating the crop.

Arabica, which originates in the highlands of Ethiopia and South Sudan, is a cool tropical plant, preferring average annual temperatures of around 19 degrees Celsius. It is thought to be more vulnerable to global warming than Robusta, which can endure up to around 23C.

The newly rediscovered Coffea stenophylla, however, can tolerate conditions similar to Robusta, but with a higher average temperature of 24.9C—more than 6C higher than Arabica, according to a study in *Nature Plants*.

Aaron Davis, Head of Coffee Research at the Royal Botanical Gardens, Kew, who led the research said that to find a coffee species with both resilience and taste is "a once in a lifetime scientific discovery". "This species could be essential for the future of high-quality coffee," he said.

Endemic to Guinea, Sierra Leone and Ivory Coast, stenophylla was considered to be superior even to Arabica according to reports from the 1800s and early 1900s, its popularity spreading to the cafes of France.

It fell out of use in the 20th century, vanishing completely from the record in 1954, until scientists finally found it growing in the wild in Sierra Leone in 2018 and set about studying its temperature tolerance—and its flavour.

Last year they carried out a blind taste test with a jury of industry professionals from coffee brands Nespresso and Jacobs Douwe Egberts. "The judges all found it different from what they know, with vegetal notes," said Delphine Mieulet, scientist at the French agricultural research centre CIRAD, who led the tasting.

The new coffee had notes of "rose, elderflower, lychee, like the best Arabica", she told AFP, adding that the sample provided was so rare that not everyone was able to taste it.

Mieulet said she was confident that the coffee would become commercially available, but said that it might take several years.

Change brewing

Having searched for stenophylla for years, Davis was aware that historical reports suggested it could be as good as Arabica.

In his book A Monograph of the Economic Species of the Genus Coffea L, published in 1925, Ralph Holt Cheney said both local people and French merchants in Sierra Leone thought the stenophylla beans were "superior to those of all other species".

"It has been shipped to France and sold as best Mocha," he wrote.

But Davis said when he was first able to taste stenophylla in August 2020, his expectations were low.

"All that changed once we'd sampled the first cup," he told AFP. "It was like expecting vinegar but then tasting fine wine. We simply did not expect it to taste that good, and were even more surprised that it tasted like Arabica."

Stenophylla is classified as vulnerable on the IUCN Red List of Threatened Species and Davis said that showed the importance of conserving the world's wild plants and biodiversity.

Researchers say more work needs to be done to work out exactly where it could adapt to be grown, but it could be in tropical areas where Arabica is already under pressure from warming.

More information: *Aaron P. Davis et al. Arabica-like flavour in a heat-tolerant wild coffee species, Nature Plants (2021).* *DOI: 10.1038/s41477-021-00891-4*

https://bit.ly/3dMaAHV

Overgrowth of gut yeast in newborns may increase asthma risk

Trans-kingdom imbalances in the gut microbes of newborns may increase the risk of asthma later in life, providing a possible target for treating the condition

An overgrowth of yeast in the gut within the first few months of life may cause changes to the immune system that increase the risk of asthma later on, shows a study published today in *eLife*.

Asthma is a common and sometimes difficult-to-manage, life-long lung condition that affects one in 10 children in developed countries. The findings explain a possible cause of asthma and may help scientists develop new strategies to prevent or treat the condition.

The period just after birth is a critical window for the development of a healthy immune system and gut microbiome. Disruptions to gut bacteria that produce anti-inflammatory compounds called short-chain fatty acids (SCFAs) early in life have previously been linked to asthma.

"We recently showed that overgrowth of a type of gut yeast called Pichia kudriavzevii in newborns in Ecuador is associated with an increased risk of asthma," says first author Rozlyn Boutin, an MD/PhD student in the Department of Microbiology and Immunology at the University of British Columbia, Vancouver, Canada. "In this study, we wanted to see if we could replicate these findings in children from an industrialised setting and identify how fungi of the gut microbiota affect the development of the immune system."

Boutin and colleagues began with a study of 123 newborns in Canada, who are part of the CHILD Cohort Study. They again found that an overgrowth of Pichia kudriavzevii in the stools of the newborns during the first three months of life was associated with a higher risk of asthma.

To understand how this yeast overgrowth might contribute to asthma later in life, the team applied Pichia kudriavzevii to newborn mice with immature gut microbiota communities. In this mouse model of asthma, the team found that the newborns exposed to the yeast experienced more lung inflammation than those who were unexposed. Applying Pichia kudriavzevii to an adolescent mouse model, however, did not cause this excess inflammation.

"Our findings show that there is a critical window in early life where disruptions in the gut microbiota caused by Pichia kudriavzevii affect the development of the immune system and increase the risk and severity of asthma later in life," Boutin says.

Previous studies have shown that bacterial SCFAs have beneficial effects on immune development that protect against asthma. In this study, the team also showed that anti-inflammatory SCFAs produced by gut bacteria inhibit the growth of Pichia kudriavzevii.

"Immune responses to gut microbe disruptions early in life have long-term consequences for diseases of the immune system later in life," concludes senior author Brett Finlay, Professor at the Michael Smith Laboratories and the Departments of Biochemistry and Molecular Biology, and Microbiology and Immunology, University of British Columbia. "Our study adds to our understanding of microbiota-associated asthma and suggests that inhibiting yeast overgrowth with SCFAs in early life could be an effective approach to preventing this condition."

https://bit.ly/3qyjavT

New biomaterial regrows blood vessels and bone, RCSI research

Scientists have developed a new biomaterial that regrows blood vessels and bone, potentially providing a single-stage approach when repairing large bone defects.

The study, led by researchers from RCSI University of Medicine and Health Sciences and SFI AMBER Centre, is published in the *Journal of Controlled Release*.

Previous RCSI-led research had found that activating a mechanosensitive gene, called placental growth factor (PGF), at different doses promoted bone regeneration and grew new blood vessels. Using this knowledge, the researchers developed a biomaterial that delivers PGF at different concentrations.

Inspired by the natural way in which bone defects regenerate, the biomaterial first releases a high dose of PGF, promoting blood vessel growth, and follows it with a more sustained lower dose, which promotes bone regeneration. When tested in a pre-clinical model, the biomaterial successfully repaired large bone defects while also regrowing blood vessels.

Current biomaterials that promote both blood vessel and bone growth typically require using more than one therapeutic drug, which means designing a more complex system that faces more challenges. Furthermore, drugs that have been approved for use in the clinic have been controversially associated with dangerous side-effects, highlighting the need for new strategies.

"More testing is needed before we can begin clinical trials, but if proven successful, this biomaterial could benefit patients when repairing bone defects by providing an alternative to current systems," said Professor Fergal O'Brien, the study's principal investigator and RCSI's Director of Research and Innovation.

"In addition to repairing bone defects, our approach to regenerative medicine executed in the study provides a new framework for evaluating regenerative biomaterials for other tissue engineering applications. We are now applying this concept of 'mechanobiology informed regenerative medicine' to identify new therapeutics in other areas, including cartilage and spinal cord repair."

The biomaterial was developed by researchers from the Tissue Engineering Research Group (TERG) based at RCSI and the SFI AMBER Centre. Their work was supported by the Irish Research

Council, the EU BlueHuman Interreg Atlantic Area Project, the European Community's Horizon 2020 research and innovation programme under European Research Council Advanced Grant agreement n° 788753 (ReCaP) and the Health Research Board of Ireland under the Health Research Awards - Patient-Oriented Research Scheme.

"By using a mechanobiology-informed approach, we were able to identify a promising new therapeutic candidate for bone repair and also determine the optimal concentrations required to promote both angiogenesis and osteogenesis within a single biomaterial," said Dr Eamon Sheehy, the study's first author and researcher in TERG.

"The regeneration of large bone defects remains a significant clinical challenge, but hopefully our new biomaterial will continue to prove beneficial in further trials."

https://bit.ly/3qDtPpc

Handwashing responsible for bacteria in sinks, largest non-hospital study shows

Handwashing is shaping communities of bacteria that live and grow in the plumbing of domestic sinks, scientists have found.

In the largest study of sink bacteria conducted outside of hospitals, scientists at the University of Reading discovered communities of similar bacteria that largely remain down our drains after hand washing.

The researchers found that there are significant differences between families of dominant bacteria depending on the location in the sink drains, and that plumbing systems such as P-trap or U-bend provides ideal environments for bacteria to grow.

Dr. Hyun Soon Gweon, Lecturer in Bioinformatics for Genomics at the University of Reading, said:

"The mantra to 'wash your hands' to fight coronavirus transmission has highlighted the importance of not only good hand hygiene, but also the need for well-designed and regularly cleaned sinks.

"Our study reveals that the significant difference in bacterial families between different buildings shows that a number of factors including occupancy and building design may have a big influence on the types of bacteria we come into contact with."

Samples were taken from 123 sinks around non-clinical settings at the University of Reading—such as toilets and bathrooms in teaching, research and social spaces—and show that sinks have a distinct microbiome dominated by certain bacteria.

The plumbing area found beneath sinks revealed microbial communities dominated by a group of bacteria called Proteobacteria. This phylum includes pathogens such as Salmonella and E. coli, which can cause serious disease, although the proportion of bacteria from that family was low. Higher concentrations were found of the common Moraxellaceae and Burkholderiaceae bacteria, which can cause infections but are mostly harmless to humans.

The type of plumbing system had a significant effect on which family was more abundant. Below- sink strainers were found to have Moraxellaceae bacteria, while P-trap sinks, which have a P-trap style of drainage, had higher amounts of Burkholderiaceae.

Lead author of the study Zoe Withey, a Ph.D. researcher at the University of Reading, said:

"The bacteria that live in our sink drains are shaped by what we are directly putting down them. While we expected that bacteria from the gut would have a greater impact, caused by the wider environment of a bathroom, it seems that by and large the bacteria living on the skin of our hands are feeding the community in the drains beneath sinks.

"This means that we need to be very aware that what we are putting down our sinks is affecting the bacterial community underneath. These areas may not be reached during routine cleaning, and this could lead to communities containing hardier, resistant microbes."

The scientists point out that all the sinks where samples were taken were regularly cleaned.

Dr. Gweon said:

"We hope our findings will remind people that the bacterial on your hands often stay alive and capable of growing even after they have been washed off, even in the presence of soap and warm water. It is possible to spread bacteria to the surrounding areas of your sink, where they can grow and persist. Reducing transmission of bacteria requires thorough disinfection of the sinks and surrounding areas and not just getting your hands wet."

The study was conducted in 2019, prior to the global pandemic caused by COVID-19 and so there is no direct influence of increased handwashing or other hygiene behaviour associated with the pandemic on this study. However, the authors point out that the significance of bacteria from the skin means that handwashing will be having a significant effect on the bacterial communities of our sinks.

More information: *Withey Z, Goodall T, MacIntyre S, Gweon H. Characterization of communal sink drain communities of a university campus. Environmental DNA. 2021;00:1-11. doi.org/10.1002/edn3.196*

https://bit.ly/3gz3Yi5

Higher mushroom consumption is associated with a lower risk of cancer

Next time you make a salad, you might want to consider adding mushrooms to it.

Hershey, Pa. -- That's because higher mushroom consumption is associated with a lower risk of cancer, according to a new Penn State study, published on March 16 in *Advances in Nutrition*.

The systematic review and meta-analysis examined 17 cancer studies published from 1966 to 2020. Analyzing data from more than 19,500 cancer patients, researchers explored the relationship between mushroom consumption and cancer risk.

Mushrooms are rich in vitamins, nutrients and antioxidants. The team's findings show that these super foods may also help guard against cancer. Even though shiitake, oyster, maitake and king oyster mushrooms have higher amounts of the amino acid ergothioneine than white button, cremini and portabello mushrooms, the researchers found that people who incorporated any variety of mushrooms into their daily diets had a lower risk of cancer. According to the findings, individuals who ate 18 grams of mushrooms --or about 1/8 to 1/4 cup-- daily had a 45% lower risk of cancer compared to those who did not eat mushrooms.

"Mushrooms are the highest dietary source of ergothioneine, which is a unique and potent antioxidant and cellular protector," said Djibril M. Ba, a graduate student in epidemiology at Penn State College of Medicine. "Replenishing antioxidants in the body may help protect against oxidative stress and lower the risk of cancer."

When specific cancers were examined, the researchers noted the strongest associations for breast cancer as individuals who regularly ate mushrooms had a significantly lower risk of breast cancer. Ba explained that this could be because most of the studies did not include other forms of cancer. Moving forward, this research could be helpful in further exploring the protective effects that mushrooms have and helping to establish healthier diets that prevent cancer.

"Overall, these findings provide important evidence for the protective effects of mushrooms against cancer," said coauthor John Richie, a Penn State Cancer Institute researcher and professor of public health sciences and pharmacology. "Future studies are needed to better pinpoint the mechanisms involved and specific cancers that may be impacted."

Paddy Ssentongo, Joshua Muscat, Robert Beelman and Xiang Gao from Penn State also contributed to this research. The researchers declare no conflicts of interest or specific funding support.

https://wb.md/2QQwh0B

Scientists Reveal How the AstraZeneca Vaccine Causes Unusual Clots

Scientists in Germany say they've worked out the two-step mechanism by which the AstraZeneca vaccine causes rare but devastating blood clots that gobble up the body's supply of platelets.

Brenda Goodman

So far, European regulators have reported more than 220 cases of unusual blood clots and low levels of platelets in patients who received the vaccine, called Vaxzevria, which was developed with funding from Operation Warp Speed as part of the race to develop a suite of vaccines to protect people from COVID-19. Vaxzevria has not yet been authorized for use in the United States.

"This is, in my opinion, rock-solid evidence," said Andreas Greinacher, MD, head of the Institute of Immunology and Transfusion Medicine, University Hospital Greifswald, Germany, who was among the first scientists in the world to link the rare clots to antibodies against the platelet factor 4 protein.

Greinacher said he found the same mechanism using three different technologies to gather evidence: dynamic light scattering, super-resolution microscopy, and electron microscopy.

"This is what scientists usually think is confirmatory evidence," he said in a call with reporters hours after publishing his study as a preprint ahead of peer review on the *Research Square* server.

Greinacher said he felt an urgent need to get the information out as soon as possible. He said his team had worked around the clock for 5 weeks to get answers, "because we are in the middle of the vaccination campaign. This was the driving force for us and the big motivation to provide these data as fast as any other possible," he told reporters on the call.

Greinacher said that he believes the mechanism linking the vaccine with the rare clotting reactions is likely to apply to other vaccines that also use adenoviruses to ferry instructions for making the virus's spike protein into cells.

"My assumption is, and that's a hypothesis, that this is a class effect of vaccines using adenovirus," he said. He added that he could not be certain because he only studied reactions to the Vaxzevria vaccine. But previous studies have shown that adenoviruses can cause the type of platelet activation he saw in the reactions he studied.

Greinacher said that he had worked out an agreement with Johnson & Johnson about an hour before the call to collaborate on studying its COVID-19 vaccine. The company had previously been unwilling to share information, he said.

At least seven cases of the same pattern of unusual clots have been documented in people who received the one-dose Johnson & Johnson vaccine, which also uses an adenovirus as its delivery vehicle. Over 7 million Johnson & Johnson vaccines have been given in the United States so far.

While the reactions are extremely rare, they can be serious. One person, a 45-year-old woman in Virginia, has died. That led the US Centers for Disease Control and Prevention and the US Food and Drug Administration to call for a pause on administering the Johnson & Johnson vaccine last week. The company also announced that it would hold clinical trials to get more answers about the reactions.

In his new study, Greinacher and colleagues describe a cascade of events that has to happen in the body before the vaccines broker these large clots. He explained that while everyone has the basic immune machinery that leads to the unusual clots, it is almost always kept in balance. The body uses a series of checks to prevent any step in the process from getting out of control.

In some cases, however, there's a perfect storm where each stage

progresses to the next and the end result is very hard to control. That autoimmune attack, which causes the body to go into a hyper-clotting state, typically burns itself out after a few weeks. So if patients can get rapid treatment, the condition nearly always goes away.

He said he only knew of one case of an autoimmune syndrome like this lasting 10 years, but that was in a patient who had taken the blood thinner heparin, which can cause a nearly identical syndrome.

Two-Step Process Leads to Clots

In the first step, the adenovirus shell in the vaccine, along with proteins from the cells where the vaccine is grown, come into contact with platelets from the blood.

Platelets are best known as colorless cell fragments that rush to the site of an infection or injury, helping the blood congeal to stop bleeding; they also play a key role in the body's immune response.

When activated, they surround invaders like bacteria and change shape to release chemical signals they store in granules.

When platelets are activated en masse, as can happen rarely after a person takes the blood thinner heparin or gets the Vaxzevria vaccine, they release a flood of these signals, Greinacher explained. These blaring signals recruit an ancient and hard-to-control branch of the immune response.

"Imagine this is like a dragon in the cave who was sleeping for a long time [but] which now got alerted by someone's throwing a stone on it," he said. The chemical signals awaken B-cells that then produce massive amounts of antibodies against the platelet factor 4 protein, which helps coordinate blood clotting.

The body erroneously thinks it is reacting to massive amounts of pathogens in the body, so the immune system overshoots. The antibodies bind the platelets, the platelets recruit white blood cells, and "then the whole thing is exploding," he said.

The second key step in these reactions is caused by EDTA, a calcium-binding agent and stabilizer that is added to the Vaxzevria vaccine. EDTA is not listed as an ingredient in the Johnson & Johnson vaccine.

EDTA opens junctions between cells that form the walls of blood vessels, causing them to become leaky. This allows the giant complexes formed by proteins and platelets to enter the blood circulation, where they — on very rare occasions — trigger that bodywide alarm.

Asked if he thought there was anything that could be done to make the vaccine safer, Greinacher said his first thought would be to try to get rid of the EDTA, which causes the second step in the process. But he said he was not a vaccine developer and didn't know how important it might be to its formulation.

Why might the Johnson & Johnson vaccine lead to similar types of clots, even though it doesn't contain EDTA? Greinacher speculated that size might play a role.

When this reaction occurs in patients who have taken heparin, the size of the heparin molecule matters. With unfractionated heparin, the longest kind of molecule, the reaction is 10 times more common than when patients take smaller low-molecular weight heparins.

Other vaccines might form smaller antibody-protein complexes that generate smaller warning signals, making the reaction less likely.

As for why the reaction appeared to be more common in women, Greinacher said he was growing skeptical that there is a large gender bias. He pointed out that most of the first vaccine recipients in Europe had been healthcare workers, who are disproportionately women.

He noted that women might be slightly more susceptible because of hormones and because women are more likely to develop autoimmune diseases, but that the risk was probably more balanced between men and women than it first seemed.

"It's not a disease of young women," he said.

Several European countries have changed or abandoned their use of the AstraZeneca vaccine.

Last week, Denmark said it would no longer include Vaxzevria as part of its vaccination program. Italy has recommended that AstraZeneca vaccine only be used in people over age 60. UK officials said people under age 30 should be offered an alternative.

Meanwhile, the European Medicines Agency said a warning about the risk of blood clots and low platelets should be added to product information for the Johnson & Johnson vaccine.

Greinacher reported grants from Deutsche Forschungsgemeinschaft during the conduct of the study and grants from Ergomed, Rovi, Sagent, Portola, Biokit, Fa. Blau Farmaceutics, Prosensa/Biomarin, DRK-BSD Baden-Würtemberg/Hessen, and Deutsche Forschungsgemeinschaft; grants and other from DRK-BSD NSTOB; grants and nonfinancial support from Boehringer Ingelheim; grants and personal fees from Macopharma; personal fees from Bayer Vital, Chromatec, Sanofi-Aventis, and GTH e.V.; and personal fees and nonfinancial support from Aspen, Instrumentation Laboratory, and Roche outside the submitted work. In addition, Greinacher reported having a patent pending for a modified SARS-CoV-2 vaccine.

Res Sq. Published online April 20, 2021. Full text

https://bit.ly/32KuHzU

Study of 'breakthrough' cases suggests COVID testing may be here to stay

So-called breakthrough cases may be driven by rapid evolution of the virus

In rare cases, people who have been fully vaccinated against COVID and are immune to the virus can nevertheless develop the disease. New findings from The Rockefeller University now suggest that these so-called breakthrough cases may be driven by rapid evolution of the virus, and that ongoing testing of immunized individuals will be important to help mitigate future outbreaks.

The research, published this week in the *New England Journal of Medicine*, reports results from ongoing monitoring within the Rockefeller University community where two fully vaccinated individuals tested positive for the coronavirus. Both had received two doses of either the Moderna or the Pfizer vaccine, with the second dose occurring more than two weeks before the positive test. One person was initially asymptomatic and then developed typical COVID-19 symptoms; the other developed symptoms prior to testing. Both individuals recovered at home, an outcome consistent with evidence suggesting vaccination is effective in preventing severe disease.

Genome sequencing revealed multiple mutations in both viral samples, including the E484K variant in one individual, first identified in South Africa and Brazil, and the S477N variant in the other individual, which has been spreading in New York since November.

"These patients got vaccinated, had great immune responses, and nonetheless broke through with a clinical infection," says Robert B. Darnell, The Robert and Harriet Heilbrunn Professor, who led the research with immunologist Michel C. Nussenzweig, virologist Paul Bieniasz, and geneticist Richard P. Lifton. The researchers were able to discern a quantifiable amount of virus in saliva samples from routine testing ongoing at Rockefeller, and sequence the viral RNA using a new coronavirus testing method developed in Darnell's lab by postdoctoral associate Ezgi Hacisuleyman with help from senior research associate Nathalie Blachere. Since January, the university has required all employees working on-site to be tested weekly using this saliva-based PCR assay.

The observations suggest what is likely a small but ongoing risk among vaccinated individuals, and the possibility that they may continue to spread the virus.

"The idea that we could be entirely done with testing in the post-vaccine world is probably not a good one right now; for example, even fully vaccinated people who develop respiratory symptoms should consider getting tested for COVID-19," says Darnell. "Conversely, exposure to individuals with known infection, even if

fully vaccinated, should be taken seriously and again individuals should consider getting tested."

"Given the scope of the pandemic, there's a huge amount of virus in the world right now, meaning a huge opportunity for mutations to develop and spread," he adds. "That is going to be a challenge for the developers of vaccines over the next months and years."

https://bit.ly/3qGIjV8

No excess mutations in the children of Chernobyl survivors, new study finds

Study found no evidence of a transgenerational effect.

By Richard Stone

Survivors of the Chernobyl nuclear disaster have long lived with a lingering fear: Did radiation exposure mutate their sperm and eggs, possibly dooming their children to genetic diseases? “Many people think if you have been irradiated, you must have effects in the next generation,” says immunologist Dimitry Bazyka, director-general of the National Research Centre for Radiation Medicine in Kyiv, Ukraine. But new findings from Bazyka and his colleagues should dispel that fear. In a study of more than 200 Chernobyl survivors and their children, the researchers found no evidence of a transgenerational effect.

The study largely resolves a major uncertainty surrounding health outcomes of the world’s worst nuclear accident, whose 35th anniversary takes place Monday. And it offers a reassuring message to evacuees from areas contaminated by Japan’s 2011 Fukushima nuclear accident. “There’s still a lot of nervousness in Japan and elsewhere about transgenerational effects,” says geneticist Stephen Chanock, director of the U.S. National Cancer Institute’s Division of Cancer Epidemiology and Genetics.

The explosion of the Chernobyl Nuclear Power Plant’s reactor No. 4 in Ukraine on 26 April 1986 and subsequent fire unleashed a plume of radioactive contamination over a large swath of Europe. Two plant workers died in the explosion and 28 firefighters died from acute radiation poisoning. For a multitude of others exposed to radionuclides, the effects have unfolded more gradually. Ionizing radiation breaks DNA; radioactive iodine spewed from the destroyed reactor triggered thyroid cancers in children and adolescents starting about 5 years after the accident. Other studies have linked exposures to cancers such as leukemia and to cardiovascular disease.

Worries about germline mutations have cast a long shadow. Parents typically pass 50 to 100 such mutations, appearing in the DNA of their sperm and eggs, on to their children. The only proven risk factor for a greater number of these so-called de novo mutations (DNMs) is a father’s age—the older he is, the more DNMs in his sperm. Although DNMs aren’t necessarily harmful, a handful have been associated with some forms of autism and other developmental disorders. Animal studies have heightened anxiety that radiation exposures mess with germ cells: Mice zapped with radiation, for example, have more DNMs than unexposed mice. But past studies haven’t yielded clear answers as to whether radiation inflicts lasting damage on human germline DNA.

About 8 years ago, Chanock struck up a collaboration with Bazyka and others to hunt for DNMs in radiation-exposed parents and their children. The team tracked down families in which the father had been involved in the perilous cleanup operation of the smoldering reactor ruins of Chernobyl or one or both parents had been evacuated hours after the accident from nearby settlements such as Pripyat, where power plant workers and their families lived.

The researchers had robust estimates of ionizing-radiation doses. Cleanup workers, men known as liquidators, wore dosimeters, and evacuee doses were reconstructed from environmental contamination assessments and by directly measuring the uptake of radioactive iodine by the thyroid gland. Doses in men ranged from

zero to 4 grays; in women, they ranged from zero to 550 milligrays. (Five grays in a single exposure can kill.)

Working with colleagues at the Broad Institute, Chanock's team sequenced the genomes of 105 parents and 130 children born between 1987 and 2002. Numbers of DNMs were no greater than those seen in the general population—even at the highest radiation doses, the researchers report today in *Science*.

"The authors have done an excellent job. Very impressive size and a very high genome coverage," says Yuri Dubrova, a geneticist at the University of Leicester who in the 1990s and early 2000s reported elevated mutation rates, in short, repetitive DNA sequences known as minisatellites in fathers living in contaminated areas near Chernobyl. Studies of even shorter repetitive sequences, known as microsatellite DNA, have yielded mixed results. Chanock's team found no evidence of a higher mutation rate in either sort of DNA.

Perhaps the mouse studies pointed to a transgenerational effect because, unlike the Chernobyl liquidators or evacuees, the mice were generally exposed to single intense bursts of radiation, Chanock says. Exposures occurring over hours or days could allow DNA repair mechanisms to eliminate excess mutations before they are passed along to children. Dubrova finds that explanation plausible. "They may be right," he says. "We don't know for how long germ cells can 'remember' the history of mutagenic insult."

Next, Chanock and Bazyka hope to track down more children of liquidators born soon after the accident—in 1987 and 1988—as well as any grandchildren.

For Bazyka, the apparent lack of a transgenerational effect offers a ray of hope in what has been a long and dark saga for Ukraine—and for him. He was in Kyiv at the time of the accident, and as a medical consultant at the interior ministry, he treated police officers whom he calls "real heroes." They enforced a safety perimeter around the reactor and suffered burns from beta particles in the radioactive dust. Ever since, Bazyka has also held a grim vigil for the liquidators, many of whom have succumbed to cancers, cardiovascular ailments, and cognitive decline. "At least," he says, "their children should be healthier than they are."

https://bit.ly/3dMEzjc

60-year scientific mystery solved

"Why would cells care about the order in which they replicate DNA?"

Over the last 60 years, scientists have been able to observe how and when genetic information was replicated, determining the existence a "replication timing program", a process that controls when and in what order segments of DNA replicate. However, scientists still cannot explain why such a specific timing sequence exists. In a study published today in *Science*, Dr. David Gilbert and his team have answered this 60-year-old question.

"Why would cells care about the order in which they replicate DNA?" asked lead scientist Dr. Gilbert. "After all - all cells need to replicate all their DNA. Our hypothesis has been that it's not just DNA that replicates, but all of the regulatory molecules that read the DNA replicate as well." Dr. Gilbert further hypothesized that there might be a purpose behind the replication timing program and process because "mother nature would not squander this opportunity to control how the DNA is read."

"The time at which you replicate provides an ideal time at which to choose whether to maintain all the regulatory factors and continue with the same functional interpretation of the information in DNA or change it to elicit new functions," explains Dr. Gilbert.

Over the last 13 years, Dr. Gilbert and his team showed that each type of cell had a unique replication timing program and that diseased cells had distinct alterations in the program. In this study, Dr. Gilbert and his team looked at how changes in the replication

timing program impact the packing of DNA with its regulatory factors, collectively known as the epigenome. The epigenome are regulatory factors that are believed to control the "identity" of the cell, and the functions that the cell will perform.

By eliminating a protein called RIF1, that helps to regulate DNA replication, they found that the replication program was severely and sometimes, almost completely gone so that all segments of chromosomes were replicating at different times in different cells. Without RIF1, if cells were prevented from replicating DNA, their epigenomes were fine. However, as soon as the DNA started to replicate, the regulatory molecules that associate with the DNA became incorporated incorrectly and worsened with each round of DNA replication. Eventually, the 3-dimensional folding of the chromosomes was also altered.

Dr. Gilbert suggests that when the epigenome is disrupted by altering the replication timing program, the cells might no longer perform their normal functions, or they may perform inappropriate functions. These inappropriate functions may have a large and negative impact on a person's health.

"We and others have shown previously that the program is altered in many diseases," says Dr. Gilbert. "Our lab recently showed specific patterns of altered timing that were linked statistically to poor outcomes in pediatric leukemia, and in another study to diseases of premature aging."

Thus, the replication timing program provides a whole new genre of molecular pathways and biomarkers that lead to and identify disease states. This could lead to earlier diagnoses and more accurate prognoses for patients.

While Dr. Gilbert's work has answered one important question, he does not plan to stop here. "We think that the epigenome... is not [only] essential for a cell to just maintain its identity, but we hypothesize that it is critical for cells to turn into other cell types."

Testing this hypothesis is crucial for the fields of stem cell research and the therapeutic application of stem cells. Dr. Gilbert is currently using human stem cells to test how a disrupted replication timing affects development of these cells into liver cells, heart cells, and neurons. The results from this study will provide valuable information for human health and disease studies in the future.

This research will appear in the 23rd April 2021 issue of the journal Science, published AAAS, the science society, the world's largest scientific organization.

https://bit.ly/3tLtZyp

Contractor that ruined 15M doses of J&J vaccine hiked price of another by 800%

FDA releases damning inspection report as lawmakers question ties to Trump admin.

Beth Mole - 4/22/2021, 9:23 PM

Things are not looking good for Emergent BioSolutions, the contract manufacturer that ruined 15 million doses of Johnson & Johnson's one-shot COVID-19 vaccine and millions more doses of AstraZeneca's COVID-19 vaccine at its production facility in Baltimore.

The Food and Drug Administration on Wednesday released a searing inspection report of the facility, finding a slew of significant violations and failings.

Meanwhile, federal lawmakers have opened a multi-pronged investigation into whether Emergent used ties to the Trump administration to get billions of dollars in federal contracts despite a history of failing to complete contracts. The investigation is also looking into inadequate staff training, persistent quality-control issues, and the company's "unjustified" 800% price increase for an anthrax vaccine.

In a letter sent to Emergent's top executives Tuesday, Rep. Carolyn Maloney, chairwoman of the House Committee on Oversight and Reform, and Rep. James Clyburn, chairman of the Select

Subcommittee on the Coronavirus Crisis, laid out the investigation, writing:

Emergent received $628 million in June 2020 to establish the primary US facility for manufacturing vaccines developed by Johnson & Johnson and AstraZeneca. Dr. Robert Kadlec, who served as Assistant Secretary for Preparedness and Response under President Trump and previously worked as a consultant for Emergent, appears to have pushed for this award despite indications that Emergent did not have the ability to reliably fulfill the contract.

800% drain

But the investigation stretches back much further than the start of the pandemic—through years of questionable federal contracts.

In 1998, Emergent (then called BioPort) bought the license to an anthrax vaccine. The vaccine, BioThrax, was approved by the FDA in 1970 but remains the only FDA-approved vaccine for anthrax. As such, Emergent is the sole supplier of anthrax vaccine for the federal government's Strategic National Stockpile (SNS). When Emergent bought the vaccine in 1998, a dose went for about $3.35. By 2010, the price was up to $28 a dose. Now, the price is over $30, and average wholesale prices are even higher, reaching $90 per dose, the lawmakers note.

"Emergent has raised the government purchasing price of the anthrax vaccine by 800% since acquiring the drug in 1998," the lawmakers write in their letter. "As a result, through most of the last decade, nearly half of the SNS's budget has been spent purchasing Emergent's anthrax vaccine. These spiraling costs contributed to shortages of critical supplies, including ventilators, reusable respirator masks, and other personal protective equipment, which severely impacted the government's ability to respond to the coronavirus crisis."

This drain on the SNS budget was particularly apparent during the pandemic—which Robert Kadlec, the former Emergent consultant, himself acknowledged.

Kadlec was nominated in 2017 by President Donald Trump to lead the Office of the Assistant Secretary for Preparedness and Response (ASPR). Following his confirmation, Emergent received millions of dollars in federal contracts from ASPR, including contracts for the SNS that were awarded without competitive bidding, the lawmakers note in their letter.

In 2020—just before the pandemic hit the US—Kadlec's office awarded Emergent around $3 billion in long-term contracts for anthrax and other bioterrorism threats. According to the lawmakers, Kadlec later suggested this was a bad move, saying, "If I could spend less on anthrax replenishment, I could buy more N95s. I could buy more ventilators. I could buy more of other things that quite frankly I didn't have the money to buy."

Failures and an inspection

Aside from the skyrocketing prices, the lawmakers suggest that Emergent didn't even deserve the contracts in the first place. In 2012, the Department of Health and Human Services awarded Emergent a $163 million contract to renovate its (currently troubled) Baltimore manufacturing plant. The idea was for the plant to become a manufacturing hub for rapidly producing vaccine in the event of an infectious disease outbreak or bioterror attack. Part of the contract stipulated that Emergent would be required to do a test run, producing 50 million doses of a pandemic influenza vaccine in the span of four months, and obtain manufacturing approval from the FDA by June 2020.

Emergent failed to meet those requirements.

Reading the FDA's inspection report of Emergent's Baltimore facility, it's clear why. During the nine-day inspection, which ended April 20, FDA inspectors logged a long list of problems at the facility.

First on the list is that Emergent failed to thoroughly investigate

how the millions of Johnson & Johnson and AstraZeneca doses became contaminated. The agency concluded that without a thorough review of what happened, it's possible that other finished batches of vaccine may also be ruined. "There is no assurance that other batches have not been subject to cross contamination," the inspectors wrote.

The FDA inspectors went on to note unsanitary conditions, paint peeling off of the walls and floors, residue on equipment, improperly trained staff, and numerous opportunities for vaccine products to be contaminated.

The potential for cross contamination—spread of viral ingredients back and forth between Johnson & Johnson's vaccine and AstraZeneca's vaccine—appeared rampant at the facility. Inspectors witnessed Emergent employees dragging unsealed, non-decontaminated bags of medical waste across different manufacturing areas. In some cases, employees tossed bags of medical waste, unsealed, into a service elevator. Emergent did not have proper written procedures for how to decontaminate waste, the inspection report notes. Security footage also caught employees moving from different areas of the facility without following proper procedures for donning and removing protective gowns.

At the request of the FDA, vaccine production at the Baltimore facility has been halted since April 16.

In a statement Wednesday, Emergent said that the FDA's findings "provide direction on the necessary steps to improve operations." The company went on:

The FDA's feedback will help us continue to improve and strengthen the supply chain for Johnson & Johnson's COVID-19 vaccine. While we are never satisfied to see shortcomings in our manufacturing facilities or process, they are correctable and we will take swift action to remedy them.

https://bit.ly/3qDlLEI

300 million-year-old 'Godzilla shark' identified as new species, gets a new name

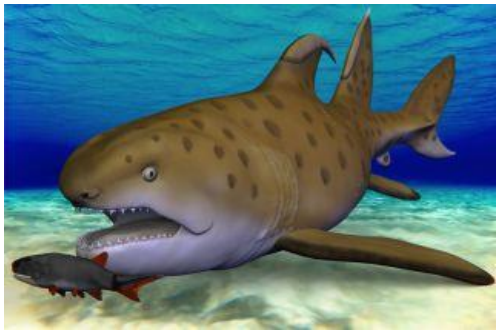
The monster-like shark was first discovered in 2013.

By Harry Baker - Staff Writer

A 300 million-year-old shark relative, nicknamed the Godzilla shark after its discovery in 2013, has finally received a proper name after being classified as its own species.

Paleontologists found the unusually complete and well-preserved 6.7-foot-long (2 meters) fossilized skeleton of the ancient shark at a private site in the Manzano Mountains near Albuquerque, New Mexico. Standout features of the skeleton include 12 rows of piercing teeth set in robust, powerful jaws, and a pair of 2.5-foot-long (0.8 m) fin spines on its back.

It was nicknamed the Godzilla shark because of its size — the skeleton is the largest fossil of its kind ever discovered in the area — and the reptilian nature of the spines on its back, John-Paul Hodnett, who first unearthed the fossil and led the new research, told Live Science.



The Godzilla shark, shown in this artistic concept illustration, would have been equipped with 12 rows of piercing teeth and a pair of 2.5-foot-long (0.8 meters) fin spines on its back. **(Image credit: Jesse Pruitt/New Mexico Department of Cultural Affairs.)**

"I am also a big fan of the Godzilla film franchise," Hodnett, a paleontologist at the Maryland-National Capital Parks and Planning Commission, said. "So when the features of this shark came to light, I thought it was the perfect nickname."

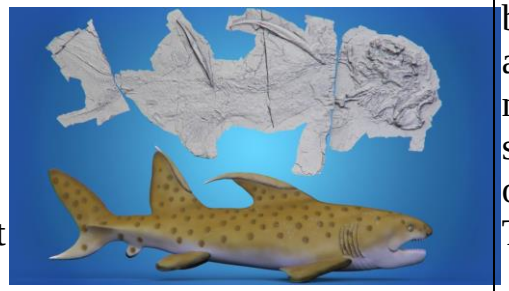
The shark has now been officially named Hoffman's dragon shark

(*Dracopristis hoffmanorum*), after the family that owned the land where the skeleton was found, and as an homage to its monstrous, reptilian appearance. "It is very rare to find skeletal material of ancient sharks, let alone a complete skeleton that also preserved the body outline and other soft tissue impressions," Hodnett said. "That and it being a new species was also amazing and unique."

Ancient Relatives

Hoffman's dragon shark belonged to a group of mysterious ancient sharks known as the Ctenacanths which diverged from modern sharks and rays around 390 million years ago during the Devonian Period. The exquisitely preserved skeleton enabled the researchers to learn more about this poorly understood group.

One of the biggest differences between the Ctenacanths and modern sharks is their jaws. "Their [Ctenacanths] jaws are larger, more firmly attached to the cranium, making them less flexible," Hodnett said.



***The fossilized skeleton of the Godzilla shark next to an artist's rendering of what it may have looked like.* (Image credit: New Mexico Museum of Natural History & Science (NMMNHS))**

These fixed jaws may mean Ctenacanths were not apex predators as modern sharks are. Instead, the new fossil suggests they may have occupied a different ecological niche.

"From the anatomy of the pectoral fins and tail we propose that *Dracopristis* was most likely a predator that kept close to the bottom of the ancient lagoon estuary it lived in," Hodnett said. "The teeth are also more adapted for grasping and crushing prey like crustaceans and small vertebrates."

The large spines on the back of Hoffman's dragon sharks may have been used as defense against larger sharks, the researchers suggest. Large shark teeth found in the area provide evidence that this is the case, according to a press statement from the New Mexico Museum of Natural History & Science (NMMNHS).

The Ctenacanths went extinct during the mass extinction event at the end of the Permian Period 252 million years ago, which brought an end to the Paleozoic Era. However, the exact cause of the sharks' demise is still unclear.

The researchers are now looking for more Ctenacanth fossils in the area to learn more about their life-history traits — evolutionary characteristics such as longevity, growth rate, age of reproductive maturity and reproductive output.

"We can't reliably reconstruct the life-history traits of a species based on one specimen alone," co-author Eileen Grogan, a biologist at Saint Joseph's University in Philadelphia, told Live Science. "A more holistic understanding of life-history traits requires greater sampling across sizes, sexes, and the environments in which the organism existed."

The study was published online April 15 in a NMMNHS Bulletin.

https://bit.ly/3nnB6uG

US military picks 3 companies to test nuclear propulsion above low-Earth orbit

General Atomics, Blue Origin and Lockheed Martin each received contracts for the Demonstration Rocket for Agile Cislunar Operations DRACO) program's first phase.

By Elizabeth Howell - Live Science Contributor

The Defense Advanced Research Projects Agency (DARPA) has picked three big space companies for the first phase of a larger project to test nuclear propulsion above low Earth orbit by 2025.

General Atomics, Blue Origin and Lockheed Martin each received contracts for the Demonstration Rocket for Agile Cislunar Operations (DRACO) program's first phase. While DARPA did not disclose the contract values in its announcement, media outlet

Space News reported General Atomics received $22 million, Lockheed Martin $2.9 million and Blue Origin $2.5 million.

The teams were selected due to their ability to develop and deploy advanced systems for reactors, propulsion and spacecraft, DARPA officials said in a statement. The agency particularly emphasized the need for "rapid maneuver" for military systems but said this is difficult in space with conventional systems.

"Current electric and chemical space propulsion systems have drawbacks in thrust-to-weight and propellent efficiency," the agency said in the same release, adding that nuclear thermal propulsion (NTP) is expected to address these common problems.

NTP systems use fission reactors that heat up propellants (such as hydrogen) to high temperatures, spewing the gas at high speed through nozzles for thrust. The thrust-to-weight ratio with NTP is about 10,000 times higher than electric propulsion systems, and propellant efficiency (also known as specific impulse) is anywhere from two to five times greater than conventional chemical rockets, DARPA officials wrote in a description of the DRACO program.

The first phase of the program has two tracks, lasting 18 months, with each company pursuing different paths. Track A includes the preliminary design of the nuclear thermal propulsion reactor, along with the propulsion subsystem. Track B will create an "operational system spacecraft concept" to meet future mission objectives, including a demonstration system.

Track A reactor development will be performed by General Atomics, while Track B work will be pursued independently by Blue Origin and Lockheed Martin, DARPA added. "DRACO's Phase 1 is expected to inform follow-on phases for detailed design, fabrication, and on-orbit demonstration. Any follow-on phases will be solicited by DARPA in a future announcement," the agency said.

This month's DARPA announcement follows on from a $14 million task order for DRACO awarded to Gryphon Technologies, a company in Washington, D.C. that provides engineering and technical solutions to national security organizations, in September 2020.

The past NASA administration also expressed interest in the potential of nuclear propulsion, especially for slicing the travel time to Mars by half to about three or four months, compared with chemical propulsion. The agency has said it hopes to get astronauts to the Red Planet in the 2030s.

"That is absolutely a game-changer for what NASA is trying to achieve," former NASA administrator Jim Bridenstine said during a meeting of the National Space Council in 2019. "That gives us an opportunity to really protect life, when we talk about the radiation dose when we travel between Earth and Mars," he added.

https://bbc.in/2QVVFCi

Malaria vaccine hailed as potential breakthrough

A malaria vaccine has proved to be 77% effective in early trials and could be a major breakthrough against the disease, says the University of Oxford team behind it.

By Philippa Roxby Health reporter

Malaria kills more than 400,000 people a year, mostly children in sub-Saharan Africa. But despite many vaccines being trialled over the years, this is the first to meet the required target. The researchers say this vaccine could have a major public health impact.

When trialled in 450 children in Burkina Faso, the vaccine was found to be safe, and showed "high-level efficacy" over 12 months of follow-up. Larger trials in nearly 5,000 children between the ages of five months and three years will now be carried out across four African countries to confirm the findings.

Malaria is a life-threatening disease caused by parasites that are transmitted to people through mosquito bites. Although preventable and curable, the World Health Organization estimates there were

229 million cases worldwide in 2019 and 409,000 deaths.

The illness starts with symptoms such as fever, headaches and chills and, without treatment, can progress quickly to severe illness and often death.

'Major health impact'

Study author Adrian Hill, director of the Jenner Institute and professor of vaccinology at the University of Oxford, said he believed the vaccine was the first to reach the World Health Organization's goal of at least 75% efficacy. The most effective malaria vaccine to date had only shown 55% efficacy in trials on African children.

The trials of this malaria vaccine started in 2019, long before coronavirus appeared - and the Oxford team developed its Covid vaccine (with AstraZeneca) on the strength of its research into malaria, Prof Hill said.

A malaria vaccine has taken much longer to come to fruition because there are thousands of genes in malaria compared to around a dozen in coronavirus, and a very high immune response is needed to fight off the disease.

"That's a real technical challenge," Prof Hill said. "The vast majority of vaccines haven't worked because it's very difficult."

However, he said the trial results meant the vaccine was "very deployable" and "has the potential to have a major public health impact".

'Tool for saving lives'

In a pre-print study with The Lancet, the research team - from Oxford, Nanoro in Burkina Faso and the US - reported the trial results of R21/Matrix-M, after testing a low and high dose of the vaccine in children, between May and August, before peak malaria season. The vaccine showed 77% efficacy in the higher-dose group and 71% in the lower-dose group.

Halidou Tinto, professor in parasitology and the principal trial investigator at the Clinical Research Unit of Nanoro, Burkina Faso, said the results were "very exciting" and showed "unprecedented efficacy levels". "We look forward to the upcoming 'phase III' trial to demonstrate large-scale safety and efficacy data for a vaccine that is greatly needed in this region."

In Africa, there have been more deaths from malaria than from coronavirus in the past year.

The Serum Institute of India, which has manufactured the vaccine, says it is confident of delivering more than 200 million doses of the vaccine as soon as it is approved by regulators. Biotechnology company Novavax provided the adjuvant for the vaccine, an ingredient which is used to create a stronger immune response.

Malaria is one of the leading causes of childhood mortality in Africa and Prof Charlemagne Ouédraogo, minister of health in Burkina Faso, said the new data showed that a new malaria vaccine could be licensed "in the coming years".

"That would be an extremely important new tool for controlling malaria and saving many lives," he said.

https://bit.ly/3nk8Glf

Body's natural pain killers can be enhanced

A study in cells and mice finds compound works with fewer side effects than opioids

Fentanyl, oxycodone, morphine--these substances are familiar to many as a source of both pain relief and the cause of a painful epidemic of addiction and death.

Scientists have attempted for years to balance the potent pain-relieving properties of opioids with their numerous negative side effects--with mostly mixed results.

Work by John Traynor, Ph.D., and Andrew Alt, Ph.D., and their team at the University of Michigan Edward F. Domino Research Center, funded by the National Institute on Drug Abuse, seeks to side-step these problems by harnessing the body's own ability to

block pain.

All opioid drugs--from poppy-derived opium to heroin--work on receptors that are naturally present in the brain and elsewhere in the body. One such receptor, the mu-opioid receptor, binds to natural pain-killers in the body called endogenous endorphins and enkephalins. Drugs acting on the mu-opioid receptor can cause addiction as well as unwanted side effects like drowsiness, problems with breathing, constipation and nausea.

"Normally, when you are in pain, you are releasing endogenous opioids, but they're just not strong enough or long lasting enough," says Traynor. The team had long hypothesized that substances called positive allosteric modulators could be used to enhance the body's own endorphins and enkephalins. In a new paper published in *PNAS*, they demonstrate that a positive allosteric modulator known as BMS-986122 can boost enkephalins' ability to activate the mu-opioid receptor.

What's more, unlike opioid drugs, positive allosteric modulators only work in the presence of endorphins or enkephalins, meaning they would only kick in when needed for pain relief. They do not bind to the receptor in the way that opioids do instead binding in a different location that enhances its ability to respond to the body's pain-relieving compounds.

"When you need enkephalins, you release them in a pulsatile fashion in specific regions of the body, then they are metabolized quickly," explains Traynor. "In contrast, a drug like morphine floods the body and brain and sticks around for several hours."

The team demonstrated the modulator's ability to stimulate the mu-opioid receptor by isolating the purified receptor and measuring how it responds to enkephalins. "If you add the positive allosteric modulator, you need a lot less enkephalin to get the response."

Additional electrophysiology and mouse experiments confirmed that the opioid receptor was more strongly activated by the body's pain-relieving molecules leading to pain relief. In contrast the modulator showed much reduced side effects of depression of breathing, constipation and addiction liability.

Their next goal is to measure their ability to enhance activation of endogenous opioids under conditions of stress or chronic pain, explains Traynor, to ensure that they are effective but don't lead to more dangerous responses like depression of breathing.

"While these molecules won't solve the opioid crisis," says Traynor, "they could slow it and prevent it from happening again because patients in pain could take this type of a drug instead of a traditional opioid drug."

Paper Cited: "Positive allosteric modulation of the mu-opioid receptor produces analgesia with reduced side effects," Proceedings of the National Academy of Sciences. DOI: 10.1073/pnas.2000017118

https://bit.ly/3aF4IOT

Inhibitory effect of strawberry geranium on inflammatory response in skin keratinocytes

Strawberry geranium (Saxifraga stolonifera) has been used in Japan as a herbal medicine to treat wounds and swelling, and continues to be an ingredient in food and cosmetics.

Pharmacological studies have shown that extracts of strawberry geranium have antioxidant and antitumor activities. However, the anti-inflammatory effect of strawberry geranium on the skin had not been well characterized.

This study, first-authored by associate professor Takeshi Kawahara of the Institute of Agriculture, Shinshu University for a joint research project with Maruzen Pharmaceutical Co., Ltd. succeeded in obtaining results which showed that the suppression of excessive immune response mediated by Toll-like receptor 2 (TLR2) to infectious microorganisms of skin keratinocytes which indicates strawberry geranium, called yukinoshita in Japanese can be a means of resolving routine infectious dermatitis.

Antibiotics against microorganisms and steroid-like components that suppress inflammation are generally used to control dermatitis, but the emergence of resistant bacteria and side effects due to chronic use are making them less desirable. Strawberry geranium provides a means to locally control inflammation on the body by provoking a limited immune response.

Strawberry geranium (Saxifraga stolonifera), called yukinoshita in Japanese.
Credit: Maruzen Pharmaceutical Co., Ltd

Yukinoshita, which means below the snow in Japanese, is a highly safe plant substance with a proven track record that has been used for centuries as foods and in cosmetics. *Saxifraga stolonifera* is also known as a crude drug and though its anti-inflammatory effect has been known, the detailed mechanism of action had not been elucidated. It is expected to be applied as an anti-inflammatory material based on the expression-suppressing effect of the TLR2 molecule clarified by this study.

Based on the results of this research, the research group is planning to conduct an efficacy test for people with mild acne. This approach has a different mechanism of action from conventional anti-inflammatory agents, but if useful results are obtained, it is expected that strawberry geranium can be widely used as an anti-inflammatory substance.

For more information on the study, please read: Inhibitory effect of strawberry geranium (Saxifraga stolonifera) on Toll-like receptor 2-mediated inflammatory response in human skin keratinocytes

https://bit.ly/3t0I7CV

Cones Derived from Human Stem Cells Help Mice See: Study

Researchers insert functioning cone photoreceptors into the retinas of mice with advanced eye disease, improving their vision.

Marcus A. Banks

Researchers report they have used retinal cone photoreceptors derived from human stem cells to restore vision in mice with advanced retinal degeneration. They are now designing a clinical trial to test whether transplanting healthy cone photoreceptors into people with age-related macular degeneration will improve their vision.

Other studies have transplanted retinal cells derived from stem cells into patients with macular degeneration, but this latest work in mice transplanted cone photoreceptors rather than retinal pigment epithelium.

“The reason we focus on cones is because they’re the most important for human vision,” says Robin Ali, who studies cell and gene therapy at King’s College London and led the study, which appeared April 20 in *Cell Reports*. Ali contrasts the role of cones, which enable us to recognize colors, discern other people’s faces, and see in a brightly lit room, to that of rods, a type of photoreceptor that works in dim light and helps with peripheral vision. While people with rod degeneration may experience tunnel vision, Ali says, people with cone degeneration may go completely blind.

The most common eye disease linked to cone decay is macular degeneration. “If you live to be old enough, you’ll have some form of macular degeneration,” Ali says. Ophthalmologists can sometimes slow the disease’s progression, but they cannot yet reverse visual decline.

Ali and colleagues wanted to know if stem cells differentiated into cone photoreceptors could restore some degree of vision in mice with inactive cones. They developed two variants of human cones: one derived from embryonic stem cells that functioned and looked normal, and a control type that appeared normal but could not respond to light. These control cones were derived from the peripheral blood of a 40-year-old person with achromatopsia, a

condition that leads to partial or complete loss of color vision.

Ali's team transplanted the cones into the retinas of mice bred to develop advanced eye disease, with completely nonfunctional cones. Using these mice controlled for the possibility that residual function from existing cones, rather than the newly transplanted cones, was responsible for any improvements in vision. To ensure that the mice did not mount an immune defense against the human cells, they were also bred to be immunodeficient.

The researchers injected functional cones into the retinas of 32 mouse eyes, and the aberrant cones into another 23 eyes. Sometimes both eyes of a mouse received the transplants, sometimes only one. Both types of cones, whether they functioned or not, attached to the retinas to form a cell mass that is typical of healthy eyes and necessary for seeing in bright light.

But the similarities ended once researchers exposed the mice to light. The retinas of mice with functional human cones responded to light during an eye test designed to measure this, known as a microelectroretinogram, while the retinas of those with dysfunctional cones did not. In another test, the mice that had received the functional cones chose to retreat to a dark room when given the option, an indication the nocturnal animals were sensing the light and avoiding it as mice typically do. Mice with deficient cones, by contrast, remained in the light for much of the time.

"I'm just impressed by the study. The kind of controls these authors have done—the lengths they have gone to make sure it is a complete, pure response to the transplanted cells, is just amazing," says Hemant Khanna, an ophthalmologist at the University of Massachusetts Medical School who was not involved in the project. Khanna says he thinks this study sets a new bar for experimental design that similar work will need to meet in the future.

"It's taken us twenty years to actually get to the point of this study, which I'm really excited about," Ali says, calling it a proof of concept that transplanted cones have the capacity to improve vision. While Ali notes that the capacity for manufacturing cones at scale does not yet exist, he is confident that his lab can produce enough cones for a human clinical trial. His next step is to recruit 16 participants in the United Kingdom in the next few years.

Ophthalmologist Sai Chavala of the University of North Texas Health Science Center points out that one concern with a stem cell–derived transplant is that it can take a while for stem cells to mature into the cells that will be transplanted. In a 2020 study in *Nature*, Chavala and colleagues showed that it is possible to convert mouse skin cells directly into photoreceptors that can be transplanted into mouse retinas, rather than first converting the skin cells into induced pluripotent stem cells. In that study, the skin cells were converted into rods rather than cones.

J. Ribeiro et al., "Restoration of visual function in advanced disease after transplantation of purified human pluripotent stem cell-derived cone photoreceptors," Cell Rep, doi:10.1016/j.celrep.2021.109022, 2021.