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Patients who had more severe covid-19 may be the best donors for convalescent plasma therapy

Study links stronger antibody responses to more severe disease, as well as more advanced age and male sex

Sex, age, and severity of disease may be useful in identifying COVID-19 survivors who are likely to have high levels of antibodies that can protect against the disease, according to a new study co-led by researchers at Johns Hopkins Bloomberg School of Public Health.

The findings suggest that older males who have recovered from COVID-19 after having been hospitalized are strong candidates for donating plasma for treating COVID-19 patients. Doctors have been using infusions of plasma--the part of blood that contains antibodies--from recovered COVID-19 patients to treat COVID-19 patients and also as a possible prophylaxis to prevent COVID-19.

Doctors have used convalescent plasma to treat patients or immunize persons at high risk of virus exposure during outbreaks of measles, mumps, polio, Ebola, and even the 1918 pandemic flu.

Clinical trials of convalescent plasma treatment against COVID-19 are ongoing, and doctors until now haven't had guidance for selecting COVID-19 survivors who are likeliest to have strong antibody responses.

"We propose that sex, age, and severity of disease should be used to guide the selection of donors for convalescent plasma transfer studies because we found that these were significant patient characteristics that not only predicted the amount of antibody but the quality of that antibody," says study lead author Sabra Klein, PhD, professor in the Bloomberg School's Department of Molecular Microbiology and Immunology.

The study, published October 19 in the *Journal of Clinical Investigation*, was a collaboration with several other research groups including that of Arturo Casadevall, MD, PhD, Bloomberg Distinguished Professor and chair of the Department of Molecular Microbiology and Immunology, and co-corresponding author Aaron Tobian, MD, PhD, professor in the Department of Pathology and director of the Transfusion Medicine Division at the Johns Hopkins School of Medicine.

For their study, the researchers tested the blood of 126 COVID-19 survivors and found high variability in their antibody levels and their antibodies' ability to neutralize the COVID-19-causing coronavirus, SARS-CoV-2. Three factors were associated with stronger antibody responses: having been sick enough with COVID-19 to be hospitalized, being older, and being male.

Initial studies of recovered COVID-19 patients have revealed a significant variability in their antibody responses to the virus--some survivors having very weak responses that would almost certainly be ineffective in helping new patients. The researchers in the new study looked for factors that might help explain some of that variability and guide clinicians to the patients most likely to have high levels of SARS-CoV-2 neutralizing antibodies.

The researchers examined samples of plasma from the 126 recovered patients using several tests. These included tests of the plasma's ability in cell cultures to neutralize cell-to-cell infection with SARS-CoV-2, as well as commercial tests for levels of antibodies to the coronavirus's spike protein--the protein that studs the surface of coronavirus particles and allows the virus to attach to and infiltrate human cells.

Consistent with several prior studies, the researchers found considerable variability among the subjects in their spike-protein antibody levels and plasma coronavirus-neutralization potency. But on average, the plasma of survivors who had been hospitalized with COVID-19 had markedly more anti-spike protein antibodies and neutralized the virus more effectively--suggesting that disease

severity prompts a stronger immune response.

"We know that the magnitude of antibody responses correlates with disease severity in other infectious diseases, such as active tuberculosis," Klein says.

Older age and male sex, which prior studies in both China and Europe have shown are associated with more severe COVID-19, were also associated with stronger antibody responses, though these links were weaker than for hospitalization status.

As part of their study, the researchers also tested study participants with commercial test kits and found that recovered COVID-19 patients who have strong neutralizing antibody responses also are very likely to have high levels of coronavirus anti-spike antibodies. This suggests that this type of test kit, which is relatively inexpensive, might be a good tool for identifying suitable plasma donors for clinical trials and treatments.

"Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population," was funded by the National Institutes of Health (U54AG062333, HHSN272201400007C, T32A1007417, AI052733, AI15207, R01AI120938, R01AI120938S1, R01AI128779, 1K23HL151826-01, R01HL059842), Bloomberg Philanthropies, and the Department of Defense (W911QY2090012).

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Hippocrates and willow bark? What you know about the history of aspirin is probably wrong

Aspirin is a good example of how myths build up around ancient medicines.

Philippa Martyr *

Aspirin is one of the most widely used drugs in the world. Its main ingredient comes from a natural product, salicin, found in plants such as willow and myrtle.

Aspirin is also a good example of how myths build up around ancient medicines.

Its origins have been closely linked with Hippocrates, the famous ancient Greek doctor and so-called father of medicine. He's said to have used willow for pain relief, inspiring the development of aspirin centuries later.

But his writings barely mention willow. So why do we still believe the myth?

What's all this about willow?

Practically every history of aspirin tells you Hippocrates prescribed willow to women in labour. Some say he prescribed willow leaf tea. Others say he told them to chew willow bark.

But when we look at what Hippocrates actually wrote, there is just one reference to burning willow leaves to make smoke for "fumigating" the uterus to get rid of a miscarried pregnancy.

This is pretty much the only reference to willow — ιτεα or *itea* — as a drug in these writings.

Could willow actually relieve pain?

Willow bark and leaves were used in some ancient medicines. However, these were often used externally, rather than swallowed. Because ancient weights and measures are confusing — and sometimes missing altogether in recipes — it's hard to tell whether there was enough salicin in an ancient recipe to make a difference.

The bark of white willow (*Salix alba*), which Hippocrates may have been talking about, doesn't contain much salicin, compared with other willows and salicin-rich plants like the myrtle tree.

A clinically effective dose of 60–120mg of salicin would be very hard to obtain from simply chewing white willow bark or drinking willow tea.

The bark of white willow doesn't contain much salicin. **Raw Pixel/Public Domain**

White willow also contains toxic, bitter-tasting tannins. These would make it hard to consume enough bark or tea to reach that

dose, and would cause stomach pain long before you got there.

Natural salicin is more abundant in other ancient plants, such as the myrtle tree. But even then you would still probably give yourself a terrible stomach ache after ingesting enough of the plant to relieve pain.

Dioscorides was an ancient Roman who wrote a guidebook of medicines, still in print today. He described willow as a remedy for stomach ache, the respiratory disease tuberculosis, and as a contraceptive.

He said if you burned willow bark, soaked it in vinegar, then rubbed it on corns and calluses, it would remove them. He also recommended a hot pack containing willow leaves for gout (which we know now as a type of arthritis).

Celsus, another Roman medical writer, said warm willow packs or poultices would treat a prolapse of the womb or bowel (where the organ literally falls out of the body). Celsus advised to push it back in, and then bandage the warm dressing on the outside.

Salicin is used today to treat corns and warts. But this doesn't mean Dioscorides' recipe worked because of the salicin. Vinegar is acidic and is said to soften corns on its own. Applying any kind of warm pack will also relieve pain.

If willow bark and leaves were handy and potent painkillers, we would have used them almost to extinction by now. Instead, by early modern times in Europe, willow was considered largely useless as a medicine. This doesn't mean willow was actually useless. It still contained salicin, but this hadn't yet been isolated or refined into its modern form.

So, if it wasn't Hippocrates, who was it?

It was English cleric Reverend Edward Stone who "rediscovered" willow.

In around 1757, Stone chewed on white willow bark out of curiosity and was struck by how bitter it was. He wondered whether it could be used medicinally, like the bitter cinchona bark (where the malaria drug quinine comes from).

Stone gathered and dried around half a kilogram of willow bark, then ground it to powder, before taking small doses every four hours to reduce his fever. Drying the bark would have concentrated the salicin, making its effect stronger.

When the powder seemed to relieve his fever, Stone tried it on his parishioners when they were sick. In 1763, he wrote to the Royal Society, reporting it worked.

How did a plant extract turn into aspirin?

Italian researchers Brugnatelli and Fontana managed to extract salicin from willow bark in 1826. Then German pharmacologist Johann Andreas Buchner created the name "salicin" in 1828 from the Latin word for willow, *salix*.

Felix Hoffmann, a researcher at the German company now known as Bayer, chemically modified the related molecule salicylic acid, which was eventually named aspirin. The company patented the name in 1899.

Today aspirin is used for pain relief, reducing swelling, lowering body temperature and preventing blood clots.

Why do we keep repeating the willow myth?

Researchers keep repeating the myth that ancient people understood the link between willow and salicin for pain relief, partly because everyone loves an epic tale. And the story of aspirin can be turned into one, with a bit of imagination. But it's a good reminder to look at original texts if you can.

It's also an example of how confirmation bias works. We know salicin is in willow, and salicin relieves pain. So when we find ancient references to willow, we think ancient people discovered salicin before us.

Modern medicine likes a respectable family tree. It helps give today's manufactured products a good pedigree. It also helps us

think of these products as safe, beneficial and part of a long healing tradition.

But the “ancient” history of aspirin has a lot of holes in it. So next time you pop an aspirin, thank Hoffmann rather than Hippocrates.

Lecturer, Pharmacology, Women's Health, School of Biomedical Sciences, University of Western Australia

Disclosure statement

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Scientists map the human proteome

Twenty years after the release of the human genome, the genetic "blueprint" of human life has now mapped the first draft sequence of the human proteome.

Twenty years after the release of the human genome, the genetic "blueprint" of human life, an international research team, including the University of British Columbia's Chris Overall, has now mapped the first draft sequence of the human proteome.

Their work was published Oct. 16 in *Nature Communications* and announced today by the Human Proteome Organization (HUPO). Overall is the only Canadian scientist involved in the *Nature Communications* paper.

"Today marks a significant milestone in our overall understanding of human life," says Overall, a professor in the faculty of dentistry and a member of the Centre for Blood Research at UBC. "Whereas the human genome provides a complete 'blueprint' of human genes, the human proteome identifies the individual building blocks of life encoded by this blueprint: proteins. "Proteins interact to shape everything from life-threatening diseases to cellular structure in our bodies."

With 90 per cent of the proteins in the human body now mapped, Overall says scientists have a deeper understanding of how individual proteins interact to influence human health, providing insights into disease prevention and individualized medicine.

Their work may have implications for scientists studying potential treatments for COVID-19.

"In COVID-19, for instance, there are two proteomes involved, that of the SARS-CoV-2 virus and that of the infected cells, both of which likely interact with, modify, and change the function of the other," says Overall. "Understanding this relationship can shed light on why some cells and individuals are more resilient to COVID-19 and others more vulnerable, providing essential functional information about the human body that genomics alone cannot answer."

As many human diseases result from changes in the composition or functions of proteins, mapping the proteome strengthens the foundation for disease diagnosis, prediction of outcomes, treatment, and precision medicine.

"Humans share 99.9 per cent of their DNA between individuals, yet deficiencies in the proteome 'parts' stemming from inherited genetic mutations can lead to genetic diseases, or defective or inadequate immune and cellular responses to environmental, nutritional and infection stressors," says Overall. "Knowing which proteins are key to protection from disease, and the deficiencies in expression or activity that are hallmarks of disease, can inform individualized medicine and the development of new therapies."

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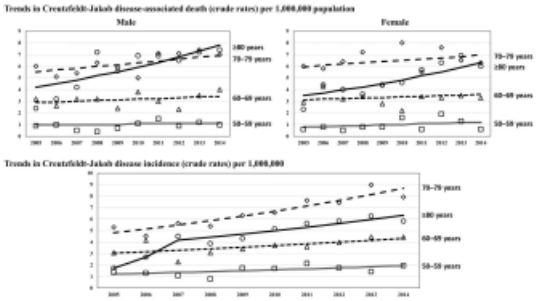
'Rare' brain disorder may not be so rare anymore, trends in japan reveal

Scientists show that incidence and mortality of a rare brain disorder in Japan almost doubled from 2005 to 2014

Creutzfeldt-Jakob disease (CJD) is a debilitating disorder that causes rapid degeneration of the brain as well as progressing dementia. It is a fatal disorder, often leading to death within just several years of the onset. CJD is the most common form of a human disorder caused by "prions," pathogenic agents that induce abnormal folding of specific cellular proteins in the brain called "prion proteins." The major type of CJD, accounting for 85% of the cases, is called sporadic CJD (sCJD). Because sCJD mainly occurs in late-middle old age, an increase in the aging population worldwide can potentially cause a rise in CJD cases, which is a pressing global concern. Thus, to help policymakers plan ahead and establish a robust strategy, it is essential to estimate the trends of CJD-associated deaths and incidence.



The trends of age-adjusted Creutzfeldt-Jakob disease (CJD) mortality rates in 2005-2014 by sex are shown (upper). The number of deaths almost doubled during this period. The incidence of CJD also doubled during this period (lower). **2020 Okayama University**

To this end, a team of researchers at Okayama University, including Dr Yoshito Nishimura, Dr Toshihiro Koyama, and Dr Hideharu Hagiya, conducted a trend analysis of the incidence and mortality of CJD in Japan, between 2005 and 2014. Their findings are published in *Scientific Reports*, a Nature Research journal. Dr Nishimura, the first author of this study, says, "Despite CJD being a rare disease, the phenomenon of population aging may trigger a rise in the incidence and, thus, the socioeconomic and healthcare burden of CJD. Our aim was to analyze these trends, in an effort to spread awareness and spur new treatment strategies."

For their analysis, the scientists used national vital statistics data on CJD-associated deaths among individuals aged over 50 years as well as the government-funded nationwide CJD surveillance data (from 2005 to 2014) in Japan. Their analysis revealed that, from 2005 to 2014, there was a significant increase in the absolute number of deaths, mortality rates, and incidence rates associated with CJD, even after adjusting for age. In particular, the average increase in incidence was estimated to be 6.4% per year. This trend in CJD-associated mortality and incidence rates was especially prominent in the older-age group, particularly in those over the age of 70 years. Although a previous report by the Creutzfeldt-Jakob Disease International Surveillance Network had stated that annual death rates of sCJD had risen in most participating countries in the past two decades, this study shows that Japan might have had higher CJD-associated deaths and incidence than other countries, which the scientists attributed to a rise in the aging population. Dr Nishimura says, "The severe socioeconomic burden on caregivers due to CJD-induced dementia warrant the attention of policymakers and stress the need for a mitigative action plan with particular focus on the increase in the prevalence of dementia. In this regard, we hope that our findings can help to guide policymakers in the right direction."

In 2015, more than 4.7 million people in Japan were living with dementia, and this number is projected to rapidly increase to 7 million by 2025. Contrary to other forms of dementia, which progress relatively slowly, patients with CJD suffer from rapidly progressing dementia. Thus, there is an urgent need to find effective strategies to improve their quality of lives and reduce the burden on caregivers. The findings of this study take a step in this direction, by shedding light on the need for effective policy measures. Dr Nishimura concludes, "CJD, albeit rare, will be more prevalent in the next 5-10 years. Policymakers and health authorities can make use of our findings to establish effective health policies."

https://bit.ly/37FdFXA

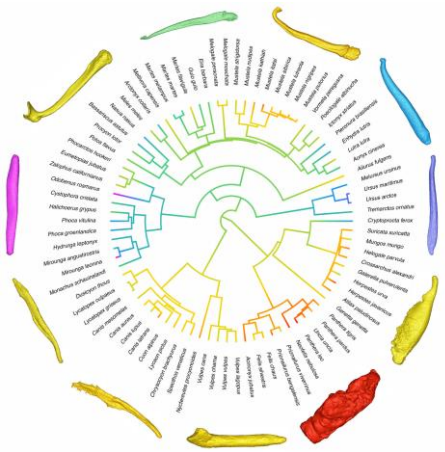
Baculum study suggests its complexity is related to monogamous behavior

Association between mammals with more highly complex baculum and monogamous sexual relationships

by Bob Yirka , Phys.org

A trio of researchers from Manchester Metropolitan University, the University of Manchester and the University of Liverpool, respectively, has found an association between mammals with more highly complex baculum and monogamous sexual relationships. In their paper published in *Proceedings of the Royal Society B*, Charlotte Brassey, Julia Behnsen and James Gardiner describe performing 3-D X-ray imaging on 82 baculum specimens from multiple species and what they found when they analyzed the images.

The baculum is a bone that resides in the penis of most mammals. Notable exceptions include horses, elephants and humans. Despite a considerable amount of research, animal scientists have not been able to figure out the purpose of the bone and why some mammals have one and others do not. In this new effort, the researchers sought to solve the mystery by scanning 82 baculum bones from a host of animal species and comparing them with one another to spot any trends.



Ancestral state reconstruction of log10 baculum complexity across Carnivora.
Credit: Proceedings of the Royal Society B: Biological Sciences (2020). DOI: 10.1098/rspb.2020.1883

In analyzing the images, the researchers found the size, shape and features of the baculum differed dramatically between species. They also found some possible clues to its purpose. They suggest the shape of many of the baculum appears to back up theories that suggest it provides assistance for longer mating sessions. And in some cases, it may provide a stimulus of sorts for the female to induce ovulation. Perhaps more intriguingly, they found that in some species, it might serve as a tool that the male can use to increase the chances of siring offspring by removing the sperm of a previous male partner. In one example, they found that the honey badger baculum was shaped very much like an ice-cream scoop, suggesting that the male could use it to scoop out the sperm of a male that had mated with the same female, and then use it as a sort of cap to push its own sperm directly through the cervix.

The researchers also found a pattern among the baculum. Those that were more complex tended to belong to males who were more monogamous. They also were not able to find any correlations between baculum complexity and shape and size of testicles.

More information: *Charlotte A. Brassey et al. Postcopulatory sexual selection and the evolution of shape complexity in the carnivoran baculum, Proceedings of the Royal Society B: Biological Sciences (2020). DOI: 10.1098/rspb.2020.1883*

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Is Lung Jelly in COVID-19 Hyaluronan, Opening Door for Treatment?

Gel-like liquid that can form in the lungs of patients with severe COVID-19 infection appears to be glycosaminoglycan hyaluronan

Liam Davenport

The gel-like liquid that can form in the lungs of patients with severe COVID-19 infection appears to be glycosaminoglycan hyaluronan (HA), Swedish researchers have discovered in findings that could pave the way for novel therapies for the disease.

"We have for the first time demonstrated a striking presence of

hyaluronan in alveolar spaces of the lungs in lethal cases of COVID-19," say Urban Hellman, PhD, Department of Public Health and Clinical Medicine, Umeå University, Sweden, and colleagues, in research published recently in the *Journal of Biological Chemistry*.

They studied lung samples obtained at autopsy from severe COVID-19 victims and compared these with lung tissue from people undergoing thoracic surgery. They found that the alveolar spaces in patients with COVID-19 were filled with exudate that stained heavily for HA, which disappeared when it was exposed to an enzyme that breaks down the polysaccharide.

"There are already therapies that either slow down the body's production of this jelly or break down the jelly through an enzyme," said Hellman in a press release from Umeå University.

"Based on this novel finding, adjuvant treatment targeting hyaluronan may be a promising approach to reduce mortality in critically ill COVID-19 patients," such as the antispasmodic hymecromone, which slows down the production of hyaluronan, the authors speculate.

They add, however, "Clinical randomized trials are warranted to evaluate the safety and efficacy of these substances in the case of severe COVID-19."

Findings May Help Explain Why Steroids Work in Severe COVID-19

As previously reported by *Medscape Medical News*, a study of more than 530 patients with COVID-19 back in June showed that those with high levels of the steroid hormone cortisol on admission to hospital have a substantially increased risk of dying.

And the RECOVERY study showed that the corticosteroid dexamethasone significantly reduced mortality among severely ill patients with COVID-19.

"It has previously been assumed that the promising preliminary results [of RECOVERY] would be linked to the general anti-inflammatory properties of cortisone," Hellman said.

"But in addition...cortisone may also reduce the production of hyaluronan, which may reduce the amount of jelly in the lungs."

Asked to comment, Venerino Poletti, MD, PhD, told *Medscape Medical News* that the current study "confirms what has already been shown in other settings in which we have acute alveolar damage...and was suspected in this context."

However, the study relies on autopsy-derived material, "which means that we are dealing with, of course, very, very severe cases, and also cases in which other confounding factors are present," including superinfections, Poletti noted.

Biopsies from living patients will be needed to help shed light on what happens in the early phases of interstitial pneumonia in patients with COVID-19, added Poletti, who is chair of the European Respiratory Society Interstitial Lung Diseases Group and professor in the Department of Respiratory Diseases and Allergy at Aarhus University Hospital, Denmark.

He nevertheless agrees with the Swedish researchers that the findings potentially shed some light on the role of steroids in treating COVID-19 infection.

However, it is not clear if these drugs can help to control hyaluronic acids "flooding into the alveolar spaces, or [whether they exert]...control of the inflammatory and vascular processes that are clearly found [as a] pathogenetic mechanism of this disease."

Another aspect to consider is that there are "at least two phenotypes" of COVID-19 infection: one in which lung compliance is preserved and another in which compliance is impaired and lung weight is increased, Poletti explained.

He suggests that in the first phenotype HA "is not present in any great quantity until the late phase," while in the second HA "plays a role in the pathogenesis."

And although this has been examined in pathophysiological studies, again, there is still a lack of biopsy data, which would be "an important step in understanding the pathogenesis of the disease."

Current Study Shows Exudate, HA Staining, in Lungs of COVID-19 Victims

For the current study, Swedish researchers examined lung tissue obtained at autopsy from three COVID-19 positive adults: two men, aged 47 and 48 years, and one woman aged 73 years.

These were compared with lung tissue from four patients undergoing thoracic surgery. The samples from all seven individuals were processed in an identical manner.

Two patients with COVID-19 had been in the exudative phase of the disease when they died, and the third was in the proliferation phase, with diffuse alveolar damage.

The alveolar spaces of all three patients with COVID-19 were filled with exudate and alveolar plugs that had pronounced HA staining. Moreover, the alveolar walls were damaged and hyperplastic, and HA staining was seen in the thickened alveolar interstitium.

The researchers say that, in contrast, the lung tissue from those undergoing thoracic surgery showed HA staining only in the alveolar walls and perivascular tissue.

Finally, they treated all the samples with hyaluronidase derived from bovine testes, which "effectively abolished the HA staining."

"It is plausible that early in the disease, when hypoxemia is developing, inhalation of hyaluronidase could possibly clear the hygroscopic macromolecule from the lungs and facilitate respiration and oxygenation," the team writes.

They also note that it "has been shown that intranasal administration of exogenous hyaluronidase can reduce lung HA content and restore lung function following influenza infection."

They add that several publications from earlier this year have also reported that the lungs of patients with COVID-19 were filled with a "clear liquid jelly," similar to that seen in "wet drowning," leading to the suggestion that it could be due to HA.

Hyaluronan levels are generally increased in response to inflammation and injury, and the HA molecule is able to absorb water up to 1000 times its molecular weight, forming a "gel-like fluid with high viscosity."

And in an editorial published earlier this year in the *Nature* journal *Cell Death & Differentiation*, Chinese researchers write: "Reducing the presence or inhibiting the production of HA holds a great promise in helping COVID-19 patients breathe. Doctors can simply provide patients medical grade hyaluronidase to reduce the accumulation of HA and thus to clear the jelly in the lung."

And they agree with Hellman and colleagues that physicians "could also try a use a clinically approved bile therapy drug, hymecromone."

The study was supported by the Swedish Heart-Lung Foundation. The authors have reported no relevant financial relationships.

J Biol Chem. Published online September 25, 2020. Full text

https://bit.ly/37zNQse

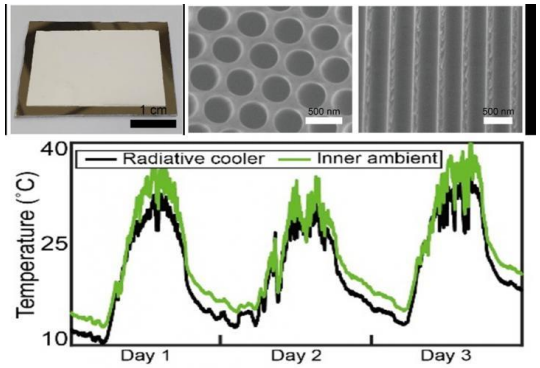
Radiative cooler that cools down even under sunlight

A daytime radiative cooling effect which exhibits lower temperatures than its surroundings even during the day

Now that autumn is upon us, there is a large temperature gap between day and night. This is due to the temperature inversion caused by radiative cooling on the Earth's surface. Heat from the sun during the day causes its temperature to rise and when the sun sets during the night, its temperature cools down. Recently, a joint research team from POSTECH and Korea University has demonstrated a daytime radiative cooling effect which exhibits lower temperatures than its surroundings even during the day.

Professor Junsuk Rho and Ph.D. candidate Dasol Lee of departments of mechanical engineering and chemical engineering

and Professor Jin Kon Kim and Ph.D. candidate Myeongcheol Go in the Department of Chemical Engineering at POSTECH have conducted a joint study with Professor Heon Lee of Materials Science Engineering at Korea University to successfully realized an energy-free radiative cooling technology using silica-coated porous anodic aluminum oxide. The study was published in the latest online edition of *Nano Energy*, an international journal in the energy sector.



Above: Photograph of fabricated radiative cooler (left). Images of the cooler captured from top (right) and cross-section (right) using the scanning electron microscope (SEM). Below: Graph of temperature measured over three days. Radiative cooler (black line) is observed to have lower temperature than its ambient temperature (green line). **Credit: POSTECH**

With growing interest in energy consumption, such as environmental pollution and limitations in using fossil fuels, attempts to lower the temperature without consuming energy continue. Radiative cooling is an example of structures installed on windows or walls to reduce the building temperature by reflecting sunlight or by absorbing and radiating far-infrared light. Radiative cooling is a technology that allows objects to receive less energy from the sun and lower temperatures by emitting radiative heat.

Unlike conventional cooling systems, radiative cooling is difficult to apply to large areas, although it has the advantage of significantly reducing energy consumption like electricity. Research to overcome this issue is being actively carried out around the world but it is still challenging to commercialize the technology.

To this, the joint research team found a very simple solution. Just by coating the porous anodic aluminum with a thin film of silica, it has been confirmed that there is a cooling effect that exhibits a lower temperature than the surroundings even under direct sunlight. Experiments have confirmed that an optimized structure can have a reflectivity of 86% in the solar spectral region and a high emissivity of 96% in the atmospheric window (8-13 μm). In addition, the radiative cooling material - produced in centimeters - showed a cooling efficiency of up to 6.1°C during the day when the sunlight was strong.

"This newly developed radiative cooling material can be easily produced," explained POSTECH Professor Junsuk Rho. He added optimistically, "It will help solve environmental problems if applied to heating and cooling systems since it can be readily applied to large areas."

This research was supported by POSCO's Green Science Program, the Future Materials Discovery Program, Mid-career Researcher, Global Frontier, Regional Leading Research Center, and the Research Leader programs of the National Research Foundation of Korea funded by the Ministry of Science and ICT of Korea and the Global PhD Fellowship from the Ministry of Education of Korea.

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Slow Lorises Are Adorable but They Bite With Flesh-Rotting Venom

Slow lorises are one of the world's only venomous mammals. Even rarer, they use their venom on one another.

By Rachel Nuwer

With their bright saucer eyes, button noses and plump, fuzzy bodies, slow lorises — a group of small, nocturnal Asian primates — resemble adorable, living stuffed animals. But their innocuous looks belie a startling aggression: They pack vicious bites loaded with flesh-rotting venom. Even more surprising, new research reveals that the most frequent recipients of their toxic bites are other slow lorises.

"This very rare, weird behavior is happening in one of our closest primate relatives," said Anna Nekaris, a primate conservationist at Oxford Brookes University and lead author of the findings,

published Monday in Current Biology. "If the killer bunnies on Monty Python were a real animal, they would be slow lorises — but they would be attacking each other."

Even before this new discovery, slow lorises already stood out as an evolutionary oddity. Scientists know of just five other types of venomous mammals: vampire bats, two species of shrew, platypuses and solenodons (an insectivorous mammal found in Cuba, the Dominican Republic and Haiti).

A male Javan slow loris named Alomah that was killed in a venomous battle with another slow loris. **Credit...Andrew Walmsley**

Researchers are just beginning to untangle the many mysteries of slow loris venom. One key component resembles the protein found in cat dander that triggers allergies in humans. But other unidentified compounds seem to lend additional toxicity and cause extreme pain. Strangely, to produce the venom, the melon-sized primates raise their arms above their head and quickly lick venomous oil-secreting glands located on their upper arms. The venom then pools in their grooved canines, which are sharp enough to slice into bone.

"The result of their bite is really, really horrendous," Dr. Nekaris says. "It causes necrosis, so animals may lose an eye, a scalp or half their face."

Before this study, many still debated the primary purpose of slow loris venom. Capturing prey was ruled out because tree gum is their primary food. That made defense against predators or parasites into leading hypotheses. But anecdotal evidence has also hinted for years that slow lorises may use their venom against their own.

For example, slow lorises are popular in the illegal pet trade. Illegal pet traders in Indonesia told Dr. Nekaris that they remove the animals' teeth not to protect future owners, but to prevent slow lorises from harming each other and ruining their price. Poachers interviewed by her also complained of sometimes capturing "ugly" slow lorises with extensive scarring or gaping wounds that they had to let go because no pet buyer would want them.

An adult male slow loris named Azka (who happens to be Alomah's father) baring its teeth, which show the toothcomb, or front lower teeth, which allow the venom to be injected. **Andrew Walmsley**

Additionally, zoo and rescue facility staff report that one of the most frequent causes of death for slow lorises is bites from other slow lorises.

To get to the bottom of how slow lorises use their venom in nature, Dr. Nekaris used radio collars to track 82 Javan slow lorises, a critically endangered species in Indonesia. Like other types of slow lorises, Javan slow lorises form long-term mating pairs that occupy small territories containing one or several gum-producing trees.

Over an eight-year span, the researchers spent more than 7,000 hours monitoring their study subjects in a two-square mile patch of forest. They recaptured the animals every few months for health checks.

Shockingly, across all captures, 20 percent of slow lorises had fresh bite wounds — oftentimes severe, flesh-rotting injuries that entailed a lost ear, toe or more. Males suffered more frequent bites than females, as did young animals dispersing from their parents' territories. While necrotic wounds were a regular occurrence, predation was not; since 2012, the researchers have lost just one Javan slow loris to a predator, which was a feral dog.

Dr. Nekaris and her colleagues concluded that slow lorises are remarkably territorial, and that they frequently use their venom to settle disputes. This puts them among just a handful of other species

known to use venom for this purpose, including cone snails, ghost shrimp and male platypuses.

The findings represent "a really cool addition to our knowledge," said Kevin Arbuckle, an evolutionary biologist at Swansea University, who was not involved in the new study.

The paper also lends unique insight into how individuals of the same species may use venom on one another to compete for limited resources such as mates or territory — something that few studies have examined, said Ronald Jenner, a venom specialist at the Natural History Museum in London, who also was not involved in the research. "To my knowledge, this is the most extensive field study ever done on this topic."

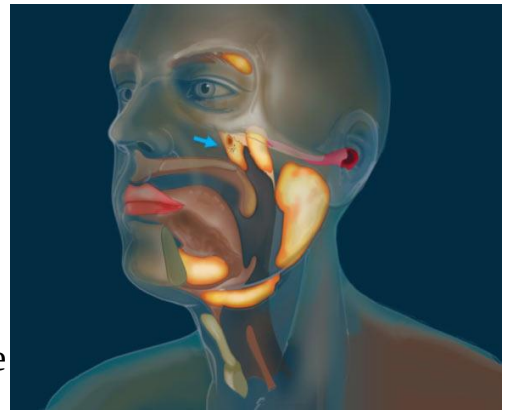
https://bit.ly/2IVqgm1

Tubarial Glands: New Organ Discovered in Human Body

Our body contains a pair of previously overlooked and clinically relevant nasopharyngeal salivary glands

Enrico de Lazaro

Our body contains a pair of previously overlooked and clinically relevant nasopharyngeal salivary glands, according to new research led by the Netherlands Cancer Institute and the University of Amsterdam. Sparing these newly-identified glands, named the 'tubarial glands,' in patients receiving radiotherapy may provide an opportunity to improve their quality of life.



This illustration shows the location of the newly-identified tubarial glands. **Netherlands Cancer Institute.**

The human salivary gland system can be divided into two separate groups: major and minor glands.

The major salivary glands are parotid, submandibular, and sublingual glands. The minor glands are distributed in groups of hundreds in the upper aerodigestive tract mucosa.

These glands produce the saliva required for mastication, swallowing, digestion, tasting and dental hygiene.

"The recently introduced molecular imaging modality of positron emission tomography/computed tomography with radio-labeled ligands to the prostate-specific membrane antigen (PSMA1 PET/CT) can visualize salivary glands with high sensitivity and specificity," said lead author Dr. Matthijs Valstar, an oral and maxillofacial surgeon in the Department of Head and Neck Oncology and Surgery at the Netherlands Cancer Institute and the Department of Oral and Maxillofacial Surgery at the University of Amsterdam, and his colleagues from the Netherlands.

"Surprisingly, we observed that PSMA PET/CT also depicted an unknown bilateral structure posterior in the nasopharynx, with ligand uptake similar to the known major salivary glands." "To our knowledge, this structure did not fit prior anatomical description."

The researchers confirmed the presence of tubarial glands in PSMA PET/CT scans of 100 patients (99 male, one female; median age 69.5; range 53-84) and the tissue of two human bodies.

"The two new areas that lit up turned out to have other characteristics of salivary glands as well," Dr. Valstar said. "We call them tubarial glands, referring to their anatomical location."

The scientists assume the physiological function of the tubarial glands is the moistening and lubrication of the nasopharynx and oropharynx.

"Radiation therapy can damage the salivary glands, which may lead to complications," said senior author Dr. Wouter Vogel, a radiation therapist in the Department of Nuclear Medicine and the Department of Radiation Oncology at the Netherlands Cancer

Institute.

“Patients may have trouble eating, swallowing, or speaking, which can be a real burden. Radiation treatment of these new glands can also go hand in hand with these complications.”

The team analyzed the data of 723 patients who had undergone radiation treatment and found that the radiotherapy dose to this area was associated with complications (xerostomia and dysphagia).

This means that the discovery is not only surprising, but it could also be a benefit to cancer patients.

“For most patients, it should technically be possible to avoid delivering radiation to this newly-discovered location of the salivary gland system in the same way we try to spare known glands,” Dr. Vogel said. “Our next step is to find out how we can best spare these new glands and in which patients. If we can do this, patients may experience less side effects which will benefit their overall quality of life after treatment.”

The team’s paper was published online September 23, 2020 in the journal *Radiotherapy and Oncology*.

Matthijs H. Valstar et al. The tubarial salivary glands: A potential new organ at risk for radiotherapy. Radiotherapy and Oncology, published online September 23, 2020; doi: 10.1016/j.radonc.2020.09.034

https://wb.md/37GuP7c

National Three-Digit Suicide Lifeline to Take Effect in 2022

Beginning in July 2022, Americans experiencing a mental health crisis will be able to dial 9-8-8 and be connected to the services and counselors at the National Suicide Prevention Lifeline.

Alicia Ault

The number was finalized when President Donald J. Trump signed the National Suicide Hotline Designation Act on October 17. It completes what has been a multiyear effort by Republican and Democratic lawmakers to make it easier for individuals to reach out during mental health emergencies.

"When your house is on fire, you can get help by calling 9-1-1," noted Rep. Seth Moulton (D-MA), a key sponsor of the legislation, in a statement. The new number "is a national step forward out of the shadows of stigma that prevent too many people from getting help and into a new era when mental health care is easy to get and normal to talk about," said Moulton, a combat veteran who has openly discussed his struggles with posttraumatic stress disorder.

The law requires the US Department of Health and Human Services to develop a strategy to provide access to specialized services for high-risk populations such as lesbian, gay, bisexual, transgender, and queer (LGBTQ) youth, minorities, and people who live in rural areas.

"This law is a historic victory, as this is the first explicitly LGBTQ-inclusive bill to pass unanimously in history — and 9-8-8 will undoubtedly save countless lives," said Sam Brinton, vice president of advocacy and government affairs for the Trevor Project, in a statement.

Brinton noted that the Trevor Project's 2020 National Survey on LGBTQ Youth Mental Health found that 40% of LGBTQ youth seriously considered attempting suicide in the past 12 months. "More than half of transgender and nonbinary youth having seriously considered it," Brinton said.

Robert Gebbia, CEO of the American Foundation for Suicide Prevention, said in a statement, "This easy-to-remember number will increase public access to mental health and suicide prevention crisis resources, encourage help-seeking for individuals in need, and is a crucial entry point for establishing a continuum of crisis care."

Gabbia called for more funding for local crisis centers to "respond to what we expect will be an increased call volume and provide effective crisis services to those in need when 9-8-8 is made

available in July 2022."

In 2017, then-Senator Orrin Hatch (R-UT) and colleague Joe Donnelly (D-IN) pushed for a three-digit number for people having mental health crises. Their legislation passed in the Senate that fall and passed in the House in July 2018.

The bill directed the Federal Communications Commission (FCC) to submit a report to Congress that would include a recommended number, a cost-benefit analysis comparing the three-digit code to the current hotline, and an assessment of how much it might cost service providers, states, local towns, and cities.

Trump signed that bill in 2018. The FCC unanimously approved the 9-8-8 number in July 2020.

Until the new number is active in July 2022, those in crisis should continue to call the National Suicide Lifeline at 1-800-273-TALK (8255).

https://wb.md/31zzTXk

Novel Evidence Suggests Apathy Is a 'Prodrome' of Dementia

A lack of interest in usual activities in older adults may be an early sign of dementia, new research shows.

Deborah Brauser

In a large, prospective study, investigators found that individuals with severe apathy at baseline had a twofold increased risk of developing dementia over a 9-year period compared to their counterparts who were not apathetic.

"This study provides novel evidence for apathy as a prodrome of dementia," the investigators, led by Meredith A. Bock, MD, clinical fellow at the University of California, San Francisco, Movement Disorder and Neuromodulation Center, write.

"We had our hypothesis about apathy, but the effect size in our study was surprisingly large — and larger than we were expecting," Bock told *Medscape Medical News.*

"More research is needed, but it's possible that [these patients] could benefit from early interventions and efforts to reduce other risk factors," she added.

The findings were published online October 14 in *Neurology.*

Separate From Depression

"Apathy, defined as decreased motivation and goal-directed behavior, is the most prevalent neuropsychiatric symptoms among the dementia subtypes," the investigators write.

They add that although apathy "is correlated with depression," it is its own unique entity. They note that about a third of patients who have both apathy and dementia do not show signs of depression.

The National Institute on Aging has flagged apathy as "a highly informative neuropsychiatric risk state," the researchers note.

However, previous research has focused on patients with mild cognitive impairment at baseline. In addition, these studies had small sample sizes and short follow-up.

"There are no large studies that have investigated apathy as an independent risk factor for or prodrome of dementia in a diverse sample of cognitively normal older adults," the researchers note.

"We think of the prodromal phase as the time when there's something abnormal going on in the brain but we can't yet detect it with our standard cognitive test. So we're thinking of other things we can ask about or look for that will give us a clue that something isn't quite right with a patient or that damage might be going on in the brain," Bock said.

The investigators assessed 2018 participants (52.3% women; 64.1% White and 35.8% Black; mean age, 74 years) in the Health, Aging, and Body Composition (Health ABC) study. All lived in the community and did not have dementia at baseline.

The current analyses' baseline was year 6 of the study. At that time point, a modified version of the Apathy Evaluation Scale was administered. Using the scores on this measure, participants were

divided into three groups on the basis of level of apathy symptoms — low (38%), moderate (37%), or severe (25%).

To evaluate cognition, the investigators administered the Modified Mini Mental State Examination (3MS) and the Digit Symbol Substitution Test (DSST) at years 5, 8, and 10.

An algorithm incorporating hospital records, use of dementia medication, and cognitive scores was used to determine incident dementia over a 9-year period. Galantamine, memantine, donepezil, rivastigmine, and tacrine were flagged as dementia medications.

Data on demographics, depression, hypertension, body mass index, cigarette and alcohol use, *APOE* genotype, and history of cardiovascular conditions, including myocardial infarction, stroke, or transient ischemic attack, were also analyzed.

Opportunity for Early Intervention?

Of the 255 participants who met criteria for clinically depressed mood, 49.5% were in the severe-apathy group, 33.5% were in the moderate-apathy group, and 17% were in the low-apathy group.

Results showed that 381 participants (18.9%) developed probable dementia during the follow-up period. In total, 25% of the severe-apathy group developed dementia, vs 19% of the moderate-apathy group and 14% of the low-apathy group.

Higher apathy was linked to a significantly higher risk of developing probable dementia in a graded manner ($P < .0001$).

The unadjusted hazard ratio (HR) for increased dementia risk for high vs low apathy was 1.9 (95% CI, 1.5 – 2.5; $P < .001$). In models adjusted for demographics, depressed mood, *APOE4* status, and cardiovascular risk factors, the HR was still a significant 1.8 (95% CI, 1.3 – 2.3; $P < .001$).

Although the HR for probable dementia in the moderate-apathy group was 1.3 (95% CI, 1.0 – 1.7; $P = .03$), the link was not significant in the fully adjusted model ($P = .06$).

At baseline, DSST scores were 1.6 points lower for the severe- vs the low-apathy group ($P = .03$), and 3MS scores were 0.9 points lower ($P = .02$).

"However, there was no association observed between the apathy groups and change in cognition over time in unadjusted or adjusted linear mixed-effects regression models," the investigators note.

In addition, no significant association was found between level of apathy and *APOE4* status, race, or sex.

"While it is possible that apathy represents a causal risk factor for dementia, likely mediated by social withdrawal, our study adds to the growing body of evidence that it is a prodromal symptom," the researchers write. The findings suggest that apathy in older individuals should be investigated, Bock added.

"Particularly if there are imaging or other biomarkers that correlate with apathy, it could be a way of finding patients early enough in the process of neurodegeneration that they would be more likely to respond to therapeutic intervention," she said.

"Novel Information"

Commenting on the findings for *Medscape Medical News*, David Knopman, MD, professor of neurology, Mayo Clinic, Rochester, Minnesota, said that the study provides some "novel information" about the relationship between apathy and cognitive impairment.

"The idea that apathy is a prodrome of developing dementia is really a very important point. That means it is part of the overall process. You wouldn't call it a risk factor; it's a prodrome because it's part of the disease," said Knopman, who was not involved with the research.

He noted that, on the basis of the results, clinicians should be aware that subtle changes in behavior can precede overt cognitive dysfunction.

If there's a sudden lack of interest in playing golf or in reading as much as was done previously, "you can't make a diagnosis on that kind of information. However, for a primary care physician, you

can file it away" and check back over time, Knopman said.

In other words, losing interest in something may not be a problem by itself but it could be a piece of the overall problem, he noted.

"Dementing illness is more than just failure on cognitive tests. It profoundly affects behavior, of which apathy or depression or anxiety are very common. And these behaviors are a core part of the disease," he added.

The study was funded by a grant from the National Institute on Aging. The investigators and Knopman have reported no relevant financial relationships.

Neurology. Published online October 14, 2020. Abstract

https://bit.ly/2HqGGf6

Genome archeologists discover path to activate immune response against cancer

Ancient embedded elements in our DNA from generations past can activate a powerful immune response to kill cancer cells like an infection.

Toronto - The work builds on Princess Margaret Senior Scientist Dr. De Carvalho's previous ground-breaking discovery known as viral mimicry-- the ability to cause cancer cells to behave as though they have been infected, thereby activating the immune system to fight cancer like an infection.

Dr. Daniel De Carvalho and his team have now identified silent ancient DNA elements buried in our genome that when 'reactivated' can initiate this immune response. Importantly, they have also discovered a key enzyme used by cancer cells to prevent this from happening in order to survive.

The enzyme is known as ADAR1, and it acts to prevent the cancer cells from signalling to the immune system. Dr. De Carvalho, Associate Professor, Medical Biophysics, University of Toronto, discovered that by inhibiting this enzyme, cancer cells were more sensitive to new drug therapies that induce viral mimicry.

The research is published online on October 21, 2020 in *Nature*, under the title, "Epigenetic therapy induces transcription of inverted SINEs and ADAR1 dependency." The study first authors are Dr. Parinaz Mehdipour, Dr. Sajid Marhon and Masters' graduate student Ilias Ettayebi, trainees in Dr. De Carvalho's laboratory.

"Humans acquired a series of 'silent' repetitive elements in our DNA over millions of years of evolution, but it has been unclear why or what purpose they serve," explains Dr. De Carvalho. "As 'genome archeologists', we set out to identify the function of these 'DNA relics' and have found that under the right conditions they can be reactivated and stimulate our immune system."

Dr. De Carvalho's discovery of ADAR1 explains how some cancer cells mount a defense against this and protect themselves from our immune system.

"These findings open up a new field of cancer therapies," says Dr. De Carvalho. "It gives us the opportunity to take advantage of these ancient repetitive DNA elements to fight cancer."

Studying the potential to modulate the immune response against tumour cells is one of the most rapidly changing and exciting areas in clinical oncology.

While much knowledge has been gained about how the immune system interacts with cancer, leading to the development of novel immunotherapy drugs, there is still a large proportion of cancer patients who do not respond to immunotherapy alone.

In Dr. De Carvalho's initial discovery, epigenetic drugs were shown to reactivate these repetitive DNA elements and lead to production of double-stranded RNA, a molecular pattern that is also observed following viral infection.

This 'viral mimicry' leads to an antiviral response directed specifically against cancer cells. In this latest research, Dr. De Carvalho's lab identified the specific ancient repetitive DNA elements as SINEs (Short Interspersed Nuclear Elements). These SINEs usually lie quiet in our genome, having little effect on the

host.

However, if activated by new epigenetic drugs, these SINES produce double-stranded RNA - a marker for infection - and can ultimately be used by cells to trigger an innate immune response.

Dr. De Carvalho likens this response "to an ancient dagger that can be used against cancer." But cancer cells are wily and have also evolved to evade detection by the immune system even under conditions where the ancient DNA sequences are activated.

Dr. De Carvalho discovered that cancer cells strike back by making more of the ADAR1 enzyme, which functions to disrupts the double-stranded RNA produced by the ancient DNA. In this way ADAR1 prevents the cancer cells from activating the immune system.

Dr. Carvalho and his team went on to demonstrate that deleting ADAR1 from cancer cells makes them exquisitely vulnerable to epigenetic drugs that induce the antiviral response.

"Since the ADAR1 activity is enzymatic, our work provides an exciting new target for drug development efforts for a completely new class of drugs that are able to exploit these 'ancient weapons' in our genome," explains Dr. De Carvalho.

The work was funded by the Canadian Institutes of Health Research, The Princess Margaret Cancer Foundation, Ontario Institute for Cancer Research, with additional support from the Princess Margaret Cancer Centre Genomics.

Competing interests

Dr. Daniel De Carvalho is co-founder and shareholder of DNAMx, Inc. and has received research funding from Pfizer and Nektar Therapeutics.

https://bit.ly/2Tq1LbL

Diagnosing Parkinson's disease with skin samples could lead to earlier detection

New research shows a simple skin test can accurately identify Parkinson's disease

Ames, Iowa - New research shows a simple skin test can accurately identify Parkinson's disease, demonstrating for the first time the feasibility of the method. Currently diagnosed by clinical signs and symptoms but only definitively diagnosed at autopsy, Parkinson's disease is commonly misdiagnosed early in the disease course, complicating clinical trials of potential treatments.

The study, published in the scientific journal *Movement Disorders*, shows how a chemical assay can detect clumping of the protein alpha-synuclein in skin samples to help diagnose Parkinson's disease (PD). The study's authors said using the assay can lead to earlier detection of PD and better clinical trials.

"Since there's no easy and reliable test available for the early diagnosis of Parkinson's disease at present, we think there will be a lot interest in the potential use of skin samples for diagnosis," said Anumantha Kanthasamy, Distinguished Professor of Biomedical Sciences at Iowa State and lead author of the study.

The researchers conducted a blinded study of 50 skin samples provided by the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND)/Brain and Body Donation Program based at Banner Sun Health Research Institute. Half of the skin samples came from patients with Parkinson's disease and half came from people without neurologic disease. Using the protein assay correctly diagnosed 24/25 Parkinson's disease patients and only 1/25 controls had the protein clumping. Dr. Charles Adler, M.D., professor of neurology at Mayo Clinic Arizona, a co-investigator of the study, notes that "these results indicate tremendously high sensitivity and specificity which is critical for a diagnostic test."

"The clinical diagnostic accuracy for early-stage PD has been quite poor, only around 50-70%. And since clinical trials really need to be done at an early stage to avoid further brain damage, they have been critically hampered because they have been including large percentages of people who may not actually have the disease," said Dr. Thomas Beach, MD, a co-investigator of the study and head of the Civin Laboratory at Banner Sun Health Research Institute.

"Improving clinical diagnostic accuracy is, in my view, the very first thing we need to do in order to find new useful treatments for PD."

The research centers on a method known as the real-time quaking induced conversion assay, a test that was originally developed to detect mad cow disease. Kanthasamy's laboratory has spent several years optimizing the assay for detecting misfolded proteins in similar human and animal disorders. Parkinson's disease arises from misfolded alpha-synuclein proteins that accumulate in the brain leading to neuronal damage. Adler and Beach have led research in AZSAND that has found these misfolded alpha-synuclein proteins also collect in other body tissues as well, including the skin.

Kanthasamy said testing skin samples could lead to earlier detection of Parkinson's disease. Earlier diagnosis could allow physicians to test therapeutic strategies designed to slow or prevent the development of advanced symptoms, he said.

https://wb.md/37yjVAt

Prepping for COVID-Flu Triage as Flu Season Begins

The set-up for primary care physicians this winter is looking worrisome.

Alicia Ault

The patient was asked a series of questions about exposure to SARS-CoV-2 before he came into the clinic. He professed no exposure. Once in the office, he told a nurse that he now recalled he'd been around a friend who had recently tested positive. The patient was alsohaving symptoms that indicated possible infection.

The nurse immediately left the room and came back in full personal protective equipment (PPE) to test him. But results weren't expected for days, which meant that multiple exposures could occur in the meantime.

That situation has been playing out in physician offices for months and likely will be repeated multiple times over as influenza season starts, said Jacqueline W. Fincher, MD, an internist in Augusta, Georgia, who had that patient in her office.

"The big issue going forward is what the volume is going to be," Fincher, president of the American College of Physicians (ACP), told *Medscape Medical News.*

Patients often don't mention symptoms during screening calls, said Gary LeRoy, MD, FAAP, a family doctor at a federally qualified health center in Dayton, Ohio. But the unrelenting presence of COVID-19 creates anxiety, he said. Patients might be in for diabetes but ask, "Can you check me for COVID?" LeRoy, president of the American Academy of Family Physicians (AAFP), said in an interview with *Medscape Medical News*.

The set-up for primary care physicians this winter is looking worrisome.

"The worst case is that you have high co-circulation of both SARS-CoV-2 and the flu, and you're using a lot of the same reagents and supplies for both of those pathogens and you run into supply chain issues or capacity issues at individual laboratories because of testing volume," Kelly Wroblewski, director of infectious diseases at the Association of Public Health Laboratories, told *Medscape Medical News*.

And Wroblewski doesn't foresee any improvement soon. "Through the end of the calendar year, we are expecting an uncomfortably tight supply chain," she said.

With predicted shortages and rapid COVID-19 tests not always available, clinicians may have to get creative.

Will Rapid Tests Help?

Physicians will want to quickly determine if a patient's symptoms are due to influenza or SARS-CoV-2.

"It sure would be nice to have that point-of-care rapid COVID test because you can tell that patient right then, 'You need to quarantine for 10 to 14 days,' " said Fincher.

But front-line physicians aren't likely to have an infinite supply of rapid COVID-19 tests at their disposal. Nursing homes, universities, large employers — like those in food production — and others are seeking the same tests.

The US Food and Drug Administration (FDA) has granted emergency use authorizations (EUAs) for four rapid, point-of-care antigen tests that detect fragments of SARS-CoV-2 in the nasal cavity. The tests are generally less sensitive than the gold standard molecular tests that use polymerase chain reaction (PCR) to measure viral DNA or RNA, according to the AAFP's COVID-19 testing guide. The antigen tests may also result in false negatives, said the AAFP.

In late August, the FDA granted an EUA for Abbott Laboratories' BinaxNOW COVID-19 Ag Card, which takes 15 minutes to deliver results and costs $5, according to the US Department of Health & Human Services (HHS).

HHS paid Abbott $760 million for 150 million tests. It is shipping those to nursing homes, congregate facilities, historically black colleges and universities, and states. HHS hopes states will use them for children in kindergarten through grade 12.

HHS Assistant Secretary Brett Giroir, MD, who leads the government's COVID-19 testing efforts, said that rapid-antigen test makers are tripling production. But the government will not facilitate COVID-19 or other test distribution to private physicians, Giroir told *Medscape Medical News*.

They will be able to get point-of-care tests "through their normal distribution channels, so we are not going to interfere with that," he said.

Rapid COVID-19 tests will soon be widely available, predicted Giroir. "We've also reviewed the orders for them, and they will be going heavily to primary care, which was their primary market before COVID," he said.

LeRoy, however, was skeptical. "The use of these tests is an individual practice choice based on availability, cost, and safety," he said.

COVID-19 Triaging Even More Critical

With the COVID-19 testing landscape unclear, physicians are considering other strategies. Vaccination is one means of keeping a lid on the spread of influenza. AAFP recommends a further ramping up of triage schemes aimed at keeping potentially infected patients out of the office.

"Many of us are not inviting people to come in to find out whether they have flu or COVID-19," said LeRoy.

Primary care physicians have been at heightened risk, as patients seem to prefer going to their doctors to see if they have COVID-19, he said.

In March and April, he did not have COVID-19 tests or enough PPE. "We couldn't get our hands on the doggone tests, no matter how hard we tried," he told *Medscape Medical News*, noting that big-volume purchasers were in line ahead of physicians and clinics. "We don't buy millions of the tests, we buy maybe hundreds," said LeRoy.

His office screens patients with questions about potential exposures and symptoms. If their temperature is higher than 100.4°F at the door, they are not allowed into the office, but are triaged there and sent to an alternative place where they can be tested for flu or COVID-19.

Fincher has a similar protocol. Patients who report acute illness or exposure by phone might be converted to a telemedicine visit or told to come to the thrice-weekly acute respiratory clinic for testing.

This fall and winter, "as much as possible, we want to take flu off the table," Fincher said. "If we don't have enough test kits for COVID, and if we don't have a turnaround time that is reasonable, like within 3 days," she said, "it becomes irrelevant."

CDC: Treat Flu Empirically

Neither AAFP nor ACP plan to issue new guidance on influenza and COVID-19. LeRoy said AAFP looks to the World Health Organization, Centers for Disease Control and Prevention (CDC), and state health departments to inform its recommendations.

The CDC updated its guidance on use of antivirals in influenza in late August, which included a section on differentiating flu and COVID-19. The agency urged physicians to steer patients with acute respiratory illness to telemedicine.

For outpatients with suspected influenza, clinicians "can consider starting early (≤ 48 hours after illness onset) empiric antiviral treatment," said the agency, even if the patient was not seen in the office.

"Clinicians should not wait for the results of influenza testing, SARS-CoV-2 testing, or multiplex molecular assays that detect influenza A and B viruses and SARS-CoV-2 to initiate empiric antiviral treatment for influenza" in priority groups, which include patients who are hospitalized, have severe, complicated, or progressive illness, or are at higher risk for flu complications.

The CDC cautioned that a positive SARS-CoV-2 test does not preclude influenza infection, and that a positive flu test does not preclude SARS-CoV-2 infection.

The FDA issued an EUA in July for a CDC multiplex molecular diagnostic that can detect and differentiate SARS-CoV-2 and influenza A and B. But the PCR-based test must be conducted in a lab certified under the Clinical Laboratory Improvement Amendments (CLIA) and will require many of the same supplies that have been experiencing shortages.

Two manufacturers, BioFire Diagnostics and Qiagen, have received EUAs for PCR-based diagnostics that detect multiple pathogens, including SARS-CoV-2 and other coronaviruses, and influenza A and B.

LeRoy said he worries about the cost of multiplex tests. "If the population at most risk can't afford the test, that's misplaced resources," he said.

Wroblewski said testing should be driven by the individual's history and what's happening in a given geographic area.

"If you have respiratory symptoms and you have no known exposure to somebody with flu or somebody with COVID, I think you want a multiplex test," said Wroblewski. But if the patient's child has the flu, then a flu test will be fine, she said. If an area has high COVID-19 case rates, the SARS-CoV-2 diagnostic is probably sufficient.

"We're going to have to be kind of nimble as we go through this respiratory season and responsive to which viruses are circulating," she said.

'No Excuse' for Lack of Tests

The public health labs — which provide "situational awareness" to state health officials and clinicians about public health threats — are also planning for how to deal with potential testing shortages, Wroblewski said.

Much of the focus for those labs is on prioritizing how much testing will be multiplex and which patients should get those tests, she said.

But physicians are not optimistic. The ACP took matters into its own hands for the lack of PPE by bulk purchasing for small practices. But it can't replicate that for diagnostics, said Fincher. She said it would be great if the federal government stepped in and ensured the testing supply is adequate.

With the advent of the Abbott tests, "it is definitely getting significantly better," Fincher said.

But, she added, "There's just really no excuse why we don't have enough tests. There's just not."

https://go.nature.com/37AR7r1

The timestamp that can tell an RNA molecule's age — to the hour

Technique allows scientists to complete a timeline for gene activity in a single cell.

An RNA-editing tool that 'timestamps' RNA molecules reveals not only which genes in a cell are turned on at any one time, but also when they were turned on.

When a gene is switched on, it triggers the production of RNA molecules that carry the information needed to make a specific protein. Scientists hoping to understand a cellular process often sequence the RNA molecules present at a given moment in a single cell. But researchers have lacked a reliable way to determine when a particular gene became active.

A team led by Edward Boyden at the Massachusetts Institute of Technology in Cambridge and Fei Chen at the Broad Institute of Harvard and MIT, also in Cambridge, tagged genes with a genetic sequence that is recognized by an RNA-editing protein. After these genes had synthesized RNA, the protein made chemical changes to the molecule, adding progressively more edits over time.

When the researchers then sequenced the RNA molecules, they could assume that those with more chemical edits were older than those with fewer edits. The system can narrow down an RNA molecule's age to within roughly one hour.

Nature Biotechnol. (2020)

https://bit.ly/34njqaC

How herpes infection may impair human fetal brain development

HSV-1 infection may contribute to various neurodevelopmental disabilities and long-term neurological problems into adulthood

Three cell-based models shed light on how herpes simplex virus type 1 (HSV-1) infection, which can spread to the fetal brain during pregnancy, may contribute to various neurodevelopmental disabilities and long-term neurological problems into adulthood, according to a study published October 22, 2020 in the open-access journal *PLOS Pathogens* by Pu Chen and Ying Wu of Wuhan University, and colleagues.

HSV-1 is a highly prevalent pathogen that can cause lifelong neurological problems such as cognitive dysfunction, learning disabilities, and dementia. But progress in understanding the role of HSV-1 in human fetal brain development has been hampered by restricted access to fetal human brain tissue as well as limitations of existing animal models. To address this gap in knowledge, the researchers generated three different cell-based neurodevelopmental disorder models, including a 2D layer of cells and a 3D brain-like structure. These models are based on human induced pluripotent stem cells (hiPSCs) - immature, embryonic stem cell-like cells that are generated by genetically reprogramming specialized adult cells.

HSV-1 infection in neural stem cells derived from hiPSCs resulted in activation of the caspase-3 apoptotic pathway, which initiates programmed cell death. HSV-1 infection also impaired the production of new neurons, and hindered the ability of hiPSC-derived neural stem cells to convert into mature neurons through a process called neuronal differentiation. Moreover, the HSV-1-infected brain organoids mimicked the pathological features of neurodevelopmental disorders in the human fetal brain, including impaired neuronal differentiation and abnormalities in brain structure. In addition, the 3D model showed that HSV-1 infection promotes the abnormal proliferation and activation of non-neuronal cells called microglia, accompanied by the activation of inflammatory molecules, such as TNF-α, IL-6, IL-10, and IL-4. According to the authors, the findings open new therapeutic avenues for targeting viral reservoirs relevant to

neurodevelopmental disorders.

The authors add, "This study provides novel evidence that HSV-1 infection impaired human brain development and contributed to the neurodevelopmental disorder pathogen hypothesis".

Research Article

Peer reviewed; Experimental study; Cells

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New study: aspirin use reduces risk of death in hospitalized patients

Hospitalized patients who were taking daily aspirin had lower risk of ICU admission, ventilation, and dying from the virus

Hospitalized COVID-19 patients who were taking a daily low-dose aspirin to protect against cardiovascular disease had a significantly lower risk of complications and death compared to those who were not taking aspirin, according to a new study led by researchers at the University of Maryland School of Medicine (UMSOM). Aspirin takers were less likely to be placed in the intensive care unit (ICU) or hooked up to a mechanical ventilator, and they were more likely to survive the infection compared to hospitalized patients who were not taking aspirin. The study, published today in the journal Anesthesia and Analgesia, provides "cautious optimism," the researchers say, for an inexpensive, accessible medication with a well-known safety profile that could help prevent severe complications.

"This is a critical finding that needs to be confirmed through a randomized clinical trial," said study leader Jonathan Chow, MD, Assistant Professor of Anesthesiology at UMSOM. "If our finding is confirmed, it would make aspirin the first widely available, over-the-counter medication to reduce mortality in COVID-19 patients."

To conduct the study, Dr. Chow and his colleagues culled through the medical records of 412 COVID-19 patients, age of 55 on average, who were hospitalized over the past few months due to complications of their infection. They were treated at the University of Maryland Medical Center in Baltimore and three other hospitals along the East Coast. About a quarter of the patients were taking a daily low-dose aspirin (usually 81 milligrams) before they were admitted or right after admission to manage their cardiovascular disease.

The researchers found aspirin use was associated with a 44 percent reduction in the risk of being put on a mechanical ventilator, a 43 percent decrease in the risk of ICU admission and - most importantly - a 47 percent decrease in the risk of dying in the hospital compared to those who were not taking aspirin. The patients in the aspirin group did not experience a significant increase in adverse events such as major bleeding while hospitalized.

The researchers controlled for several factors that may have played a role in a patient's prognosis including age, gender, body mass index, race, hypertension and diabetes. They also accounted for heart disease, kidney disease, liver disease and the use of beta blockers to control blood pressure.

COVID-19 infections increase the risk of dangerous blood clots that can form in the heart, lungs, blood vessels and other organs. Complications from blood clots can, in rare cases, cause heart attacks, strokes and multiple organ failure as well as death.

Doctors often recommend a daily low-dose aspirin for patients who have previously had a heart attack or stroke caused by a blood clot

to prevent future blood clots. Daily use, however, can increase the risk of major bleeding or peptic ulcer disease.

"We believe that the blood thinning effects of aspirin provides benefits for COVID-19 patients by preventing microclot formation," said study co-author Michael A. Mazzeffi, MD, Associate Professor of Anesthesiology at UMSOM. "Patients diagnosed with COVID-19 may want to consider taking a daily aspirin as long as they check with their doctor first." Those at increased bleeding risk due to chronic kidney disease, for example, or because they regularly use certain medications, like steroids or blood thinners, may not be able to safely take aspirin, he added.

Researchers from Wake Forest School of Medicine, George Washington University School of Medicine, Northeast Georgia Health System, and Walter Reed National Military Medical Center also participated in this study.

"This study adds to the tremendous work our researchers are doing in the School of Medicine to help find new treatments against COVID-19 and save patients' lives," said E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. "While confirmatory studies are needed to prove that aspirin use leads to better outcomes in COVID-19, the evidence thus far suggests that patients may want to discuss with their doctor whether it is safe for them to take aspirin to manage potentially prevent serious complications."

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A dead end on the way to the sky

Little bat-like dinosaurs could glide — but only just.

It is one of the enduring wonders of evolution that natural selection can produce complex traits such as flight. But that doesn't mean every evolutionary journey ends with a falcon's speed or a swallow's aerial acrobatics.

Alexander Dececchi at Mount Marty University in Yankton, South Dakota, and his colleagues analysed the fossilized remains of two species of feathered dinosaur, *Yi qi* and *Ambopteryx longibrachium*. Both lived in what is now China some 160 million years ago, and both weighed less than one kilogram.

The feathered dinosaur Ambopteryx longibrachium (artist's impression) was inept at gliding and incapable of powered flight. **Gabriel Ugueto**

These little reptiles might have been able to glide — poorly. Laser-stimulated fluorescence, an imaging technique that uses lasers to excite atoms, which then emit light, revealed details of the skin between *Yi qi*'s elongated digits that suggest the creature had membranous wings. Mathematical models of the performance of these 'wings' suggest that the dinosaurs would have been able to glide only short distances and that they are unlikely to have been capable of flapping or powered flight. They probably walked relatively slowly on the ground and therefore lived their lives in trees.

Perhaps unsurprisingly, this lineage quickly went extinct, leaving the skies to the ancestors of today's birds. *iScience (2020)*

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Like humans, male chimps mellow with age

Data on chimpanzees suggest they, too, develop more meaningful friendships as they age

By Lucy Hicks

For all its drawbacks, aging brings a benefit: Social relationships generally improve. Older individuals have fewer but closer friendships, avoid conflicts, and are more optimistic compared with younger adults. Now, 20 years of data on chimpanzees suggest they,

too, develop more meaningful friendships as they age.

The finding challenges a long-standing assumption that humans mellow with age because we are aware of our approaching mortality. Simply put, "You don't have time for all this negativity in your life, so you shift toward more positive thinking," says Zarin Machanda, a primatologist at Tufts University and an author of the new study. But finding the same pattern in chimps suggests a simpler explanation: It could be an evolved trait found in a wider range of species. The new study "should make us think twice" about the roots of some human behaviors, says Ian Gilby, a behavioral ecologist at Arizona State University, Tempe, who was not involved in the work.

Machanda and colleagues gathered data from the Kibale Chimpanzee Project, which has tracked wild chimpanzee behavior in Uganda's Kibale National Park since 1987. Because chimps are socially similar to humans—they live in large groups and engage in both cooperative and antagonistic relationships throughout their lives—they serve as an ideal test group for studying changes in social behavior. The researchers zeroed in on the males, who had more purely peer-to-peer relationships than females.

Combing through 21 years of behavioral logs on 21 chimps aged 15 through 58, the researchers found that older males (aged 35 and up) had more mutual friendships than younger ones, they report today in *Science*. Older "friends" would sit together and groom one another on a regular basis, whereas younger chimps were more likely to engage in one-sided relationships, in which they groomed preferred elders who rarely returned the favor.

That makes sense to Gilby, who suspects that younger males groom older, dominant ones to rise in the group hierarchy. But as males age and fall in rank, they stop competing for dominance and "tend to give up," he says. Forming these cooperative relationships with peers could help older males maintain their status, helping them fend off challenges by younger and fitter chimps.

The researchers also found that older males had fewer aggressive interactions with other members of the group. "They're not getting drawn into scuffles all the time, in the way a younger chimpanzee might be," says Alexandra Rosati, a psychologist at the University of Michigan, Ann Arbor, and an author of the study.

The findings wouldn't surprise most primatologists, says Gilby, who has observed these types of one-sided and mutual male relationships during field research. But the evidence that we and our closest relatives share a social aging pattern challenges the idea that these behaviors are uniquely human. Rather than being tied to our mortality, they could be an adaptive response that improves the mating success or group rank of older chimps.

Rosati is eager to see whether other chimpanzee groups—and female chimpanzees—also experience this mellowing with age. She says the theory could also be tested in other long-lived social species, like bonobos, elephants, and orcas. Next, however, she and Machanda will take a deeper look at how social bonds might benefit aging chimps—and whether the same mechanisms could be at work in humans. "There is a lot more to learn," Gilby says.

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Alien Planets Around 1,000 Nearby Stars Could Be Looking Straight Back at Earth

Two researchers are looking at which exoplanets are getting a good view of Earth. It turns out there are 1,004

David Nield

Astronomers are working hard to catalogue all of the exoplanets visible from Earth, but now two researchers have turned the idea around, to look at which exoplanets are getting a good view of Earth in return.

It turns out there are 1,004 (and counting) main sequence stars, similar to the Sun, with orbiting Earth-like planets that probably

have an opportunity to detect chemical traces of life on our own planet. If there's anyone up there, they can see us.

These stars are all within 326 light-years (100 parsecs) of Earth, with the study focusing on the closest exoplanets first. Data from NASA's Transiting Exoplanet Survey Satellite (TESS) star catalogue and the Gaia star map was used to make the calculations, and over time the star systems that can view Earth will change.

"If observers were out there searching, they would be able to see signs of a biosphere in the atmosphere of our Pale Blue Dot," says astronomer Lisa Kaltenegger, from Cornell University. "And we can even see some of the brightest of these stars in our night sky without binoculars or telescopes."

To spot Earth, astronomers on these exoplanets would need to use the same techniques we do to catalogue a distant object: watching as Earth passes in front of the Sun to figure out the makeup of our planet's atmosphere, known as a transit observation.

The Earth's ecliptic, or the plane of Earth's orbit around the Sun, is crucial in working out which exoplanets can see us. It tells astronomers where exoplanets with a good view of Earth are going to be located – in other words, from which deep space vantage points our spinning rock will appear as a transiting planet.

Of the 1,004 stars identified with potential habitable zones, 508 offer their surrounding planets a minimum of a 10-hour observation window of Earth with each orbit. Most of the stars – 77 percent – are M-type or red dwarf stars, the smallest and the coolest of main sequence stars.

"Only a very small fraction of exoplanets will just happen to be randomly aligned with our line of sight so we can see them transit," says physicist Joshua Pepper, from Lehigh University. "But all of the thousand stars we identified in our paper in the solar neighbourhood could see our Earth transit the Sun, calling their attention."

The TESS space telescope has already proved phenomenally useful since it went into operation in 2018: it's been busy identifying our next-door neighbours in space, and solving mysteries about the edges of our Solar System, as well as looking for the most Earth-like exoplanets in the cosmos.

When the NASA James Webb Space telescope finally launches, studying space in the infrared spectrum, it will give us even more information about the composition of exoplanets and the story of the early universe.

For now the researchers think their work could be used to narrow down the search for extraterrestrial life in the future – if we want to find exoplanets that might have spotted us as well as us spotting them, for example.

"If we found a planet with a vibrant biosphere, we would get curious about whether or not someone is there looking at us too," says Kaltenegger. "If we're looking for intelligent life in the universe, that could find us and might want to get in touch, we've just created the star map of where we should look first."

The research is due to be published in *Monthly Notices of the Royal Astronomical Society: Letters*.

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The unexpected repair function of neutrophils

CNIC scientists have discovered previously unsuspected actions of the immune system that help to maintain organ health

Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have discovered that neutrophils, the most abundant cells of the innate immune system, have many more functions in the body than previously thought. This finding suggests possible new treatments for many diseases, including cancer.

In a study published in the journal *Cell*, the research team demonstrate that neutrophils acquire new characteristics when they arrive in a tissue and that these specialized functions help to

maintain organ health.

The cells of the immune system defend the body against external pathogens, providing protection against microorganisms that cause disease, while also helping to repair injuries such as wounds and bone fractures.

The different types of immune cells include lymphocytes and the cells of the innate immune system. "Lymphocytes produce antibodies or receptors that specifically target viruses or bacteria to build immunity against these pathogens. The cells of the innate immune system, on the other hand, provide a faster but nonspecific response that can sometimes trigger uncontrolled inflammation, as happens in the lungs of patients with severe COVID-19, for example," explained Dr Andrés Hidalgo, lead investigator on the study.

Every day, the marrow inside our bones produces immense quantities of neutrophils. These cells then enter the bloodstream and are distributed to almost all tissues of the body. Neutrophils have a short lifespan, living for less than 24 hours. For this reason, scientists believed that these cells had a very limited capacity to adapt to their environment and adopt new functions.

But in the *Cell* study, "we found that when neutrophils leave the circulation and migrate into tissues they acquire new, previously unknown properties", said Dr Hidalgo.

"What is fascinating is that neutrophils appear to acquire functions useful to the specific tissues in each organ. For example, we found that neutrophils in the lung acquire the ability to contribute to the formation of blood vessels, whereas neutrophils in the skin help to maintain the integrity of the cutaneous epithelium. This ability to change cell properties was identified in healthy individuals, which suggests that neutrophils participate in a great variety of normal functions in the body and are not limited to combating infection," said Dr Hidalgo.

Historically, scientists have viewed the innate immune system as a collection of cells with fixed, nonspecific responses. But in recent years, some researchers have found evidence that these cells can acquire highly specific functions. According to co-lead investigator and first author Iván Ballesteros, "this is particularly exciting because if we can define the mechanisms that control how these cells acquire new functions we will be able to design new treatments to exploit this plasticity of neutrophil responses for the benefit of patients."

In cancer, for example, tumors need to promote the generation of new blood vessels in order to grow. To block tumor growth, scientists therefore need to understand how tumors co-opt the plasticity of the immune system to promote the formation of these blood vessels. For Ballesteros, a major point of interest in the new study is that "the results show that neutrophil immune plasticity is not dependent on the presence of disease, suggesting that it has beneficial functions that sometimes get short-circuited in pathological settings."

Previous studies had already identified neutrophil heterogeneity in several diseases. Indeed, these neutrophil changes are prognostic markers in cancer and help to regenerate blood cells after bone marrow transplantation.

However, the mechanisms that establish neutrophil hyperplasticity are poorly understood, and the new results are a crucial step towards filling this knowledge gap. "Essentially, what we have demonstrated is that neutrophils, despite their sort lifespan, can change their function and that they do this when they enter tissues. The identification of these adaptations allows a better understanding of the roles of different immune cells in disease," explained Andrea Rubio, joint first author on the study and a bioinformatician at the CNIC.

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Researchers Discover a Second 'Key' That Makes The New Coronavirus So Infectious

We're now a little closer to solving, with researchers uncovering yet another way the virus gains entry into our cells

Mike Mcrae

It's been 17 years since the coronavirus SARS-CoV threatened to erupt into a global pandemic. Thanks to rapid efforts to contain outbreaks of the infection, the world's population was spared the worst.

This time we weren't so fortunate. Just what makes SARS-CoV-2 so much more infectious than its predecessor is a question we're now a little closer to solving, with researchers uncovering yet another way the virus gains entry into our cells.

Researchers from the Technical University of Munich in Germany and the University of Helsinki in Finland led a study that discovered a receptor called neuropilin-1 gives the novel coronavirus a leg-up in infecting our tissues.

This particular protein is relatively abundant on cells lining the nasal cavity, making it a piece of cake for the virus to establish a home inside our bodies, raise a virus family, and then spread to a new host.

Earlier this year it was discovered that a receptor called angiotensin-converting enzyme 2 (ACE2) helps the coronavirus bind to the surface of cells, while an enzyme called Type II transmembrane serine protease (TMPRSS2) is crucial for it gaining entry.

This kind of molecular lock-picking does a good job of explaining why both SARS coronaviruses wreak havoc throughout a range of tissues in our bodies, from the lining of our lungs to our digestive tract. But it doesn't say why one of the viruses does a better job of spreading than the other.

"The starting point of our study was the question why SARS-CoV, a coronavirus that led to a much smaller outbreak in 2003, and SARS-CoV-2, spread in such a different way even if they use the same main receptor ACE2", says University of Helsinki virologist Ravi Ojha.

A crucial piece of the puzzle appeared on comparing the two viral genomes; SARS-CoV-2 had picked up sequences responsible for producing a prickly array of 'hooks', not unlike those used by other nasty pathogens to grip onto host tissues.

"Compared to its older relative, the new coronavirus had acquired an 'extra piece' on its surface proteins, which is also found in the spikes of many devastating human viruses, including Ebola, HIV, and highly pathogenic strains of avian influenza, among others," says Olli Vapalahti, also a virologist from the University of Helsinki. "We thought this could lead us to the answer. But how?"

Consulting with colleagues around the world, the researchers zeroed in on neuropilin-1 as a common factor.

Typically, this receptor plays a role in responding to growth factors important in tissue development, especially among nerves. But to many viruses, it's a convenient handle for holding onto host cells long enough to break in. Electron microscopy of the surface spikes coating SARS-CoV-2 particles certainly hinted at the potential for a relationship with the receptor.

To help confirm it, the researchers made use of monoclonal antibodies specifically selected to block access to garden variety neuropilin-1, but not to mutant varieties tweaked to have a slightly different structure.

Sure enough, 'pseudoviruses' sporting SARS-CoV-2 proteins (great for watching viruses enter cells without worrying about the whole messy replication business that follows) had a much harder time getting inside when neuropilin-1 was locked up.

"If you think of ACE2 as a door lock to enter the cell, then

neuropilin-1 could be a factor that directs the virus to the door," says Balistreri. "ACE2 is expressed at very low levels in most cells. Thus, it is not easy for the virus to find doors to enter. Other factors such as neuropilin-1 might help the virus finding its door."

With neuropilin-1 expressed in large amounts in nerve tissues within the nasal cavity, we might imagine SARS-CoV-2 has a convenient red carpet rolled out for it the moment we sniff an infected droplet.

A close look at tissue samples expressing neuropilin-1 taken from deceased COVID-19 patients added to suspicions, while an experiment involving mice helped confirm the receptor's role in assisting the virus's entry into our nervous system.

Whether this might help explain why SARS-CoV-2 infections can have such a traumatic impact on the brain's function is a question for future research.

"We could determine that neuropilin-1, at least under the conditions of our experiments, promotes transport into the brain, but we cannot make any conclusion whether this is also true for SARS-CoV-2. It is very likely that this pathway is suppressed by the immune system in most patients," says neurologist Mika Simons from the Technical University of Munich.

It's tempting to picture new forms of antiviral medication on the horizon. Though as rapidly as SARS-CoV-2 reveals its criminal talents, simply blocking off cell receptors is likely to be bad news for our health.

That's not to say the discovery isn't without opportunity.

"Currently our laboratory is testing the effect of new molecules that we have specifically designed to interrupt the connection between the virus and neuropilin," says Balistreri.

"Preliminary results are very promising and we hope to obtain validations *in vivo* in the near future."

This research was published in *Science*.

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Large tides may have been a key factor in the evolution of bony fish and tetrapods

Large tides may have been a key environmental factor in the evolution of the first vertebrate land-dwellers

Pioneering research, published in *Proceedings of the Royal Society A*, into ancient tides during the Late Silurian—Devonian periods (420 million years ago—380 million years ago), suggests that large tides may have been a key environmental factor in the evolution of bony fish and early tetrapods, the first vertebrate land-dwellers.

Credit: The Field Museum of Natural History in Chicago

The study is a detailed development of a theory previously published in the same journal, which suggested that the Moon's particular mass and orbital location are optimized for creating large tidal ranges and isolating tidal pools, which in turn may have been a biological impetus for the development of limbs in fish stranded between very high tides.

First detailed numerical simulations

Researchers from Bangor University and Oxford University in the UK and Uppsala University in Sweden have been the first to produce detailed numerical simulations to address the question of whether large tides occurred during this critical period. These are also the first calculations to relate tidal hydrodynamics to an evolutionary biological event.

The numerical simulations were computed using palaeogeographic reconstructions of the Earth's continents in an established state-of-the-art numerical tidal model. The simulation results show tidal variations in excess of four meters occurring around an area known

as the South China block, which is the site of the origin and diversification of the earliest bony fish group, and has produced the earliest important fossils for this group. Geological evidence also points to tidal environments being closely associated with this class of fossils.

These first-of-their-kind results stimulate the need for more detailed tidal simulations of the ancient Earth. In particular, the researchers believe that the method used in this study can be used with a variety of palaeogeographic reconstructions at other time periods, to explore the tidal influence upon the origin and diversification of other early vertebrates, and perhaps the opposite as well: what might have been the role of tides in precipitating marine extinction events?

More information: *H. M. Byrne et al. A key environmental driver of osteichthyan evolution and the fish-tetrapod transition?, Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences (2020). DOI: 10.1098/rspa.2020.0355*

https://bit.ly/3md7NZU

Ancient Maya Used Zeolite and Quartz to Filter Drinking Water

Oldest known example of water purification in the western hemisphere and the oldest known use of zeolite for decontaminating drinking water in the world

Tikal, an ancient Maya city in what is now northern Guatemala, is one of the largest political, economic and military centers of the pre-Columbian Maya civilization. The metropolis was inhabited from the 6th century BCE to the 10th century CE, and had a population of up to 90,000 people in its heyday. A large reservoir called the Corriental reservoir was an important source of drinking water for the city. A team of archaeologists from the University of Cincinnati has found that between about 2,200 and 1,000 years ago, the drinking water in this reservoir was filtered through a mixture of zeolite and coarse, sand-sized crystalline quartz. This filtration system is the oldest known example of water purification in the western hemisphere and the oldest known use of zeolite for decontaminating drinking water in the world.

Zeolite is a non-toxic, porous, crystalline, hydrated aluminosilicate mineral with natural adsorbent and ion exchange properties, which removes harmful microbes as well as dispersed insoluble and soluble toxins from drinking water.

The ancient Maya city of Tikal in northern Guatemala. **Gerd Eichmann / CC BY-SA 4.0.**

Approximately 2,700 years ago, Greek and Roman engineers used zeolites as a pozzolan in cement in the construction of large scale hydraulic structures such as aqueducts, bridges, dams, and harbors.

However, it has been assumed that zeolites were not used for water purification until the beginning of the 20th century.

It also has been presumed that the oldest forms of water purification occurred in Europe and southern Asia.

“The ancient Maya created their water filtration system nearly 2,000 years before similar systems were used in Europe, making it one of the oldest water treatment systems of its kind in the world,” said lead author Dr. Kenneth Barnett Tankersley, a researcher in the Department of Anthropology and the Department of Geology at the University of Cincinnati.

“What’s interesting is this system would still be effective today and the Maya discovered it more than 2,000 years ago.”

Dr. Tankersley and colleagues used X-ray diffraction analysis to identify zeolite and crystalline quartz in the sediments from the Corriental reservoir.

They traced these minerals to steep ridges around the Bajo de Azúcar about 18 miles northeast of Tikal.

“It was an exposed, weathered volcanic tuff of quartz grains and

zeolite. It was bleeding water at a good rate," said co-author Professor Nicholas Dunning, a scientist in the Department of Geography and GIS at the University of Cincinnati.

"Workers refilled their water bottles with it. It was locally famous for how clean and sweet the water was."

The zeolite filtration system would have protected the ancient Maya from harmful cyanobacteria and other toxins that might otherwise have made people who drank from the reservoir sick.

"The ancient Maya figured out that this material produced pools of clear water," said co-author Dr. David Lentz, a biologist in the Department of Biological Sciences at the University of Cincinnati.

"Complex water filtration systems have been observed in other ancient civilizations from Greece to Egypt to South Asia, but this is the first observed in the ancient New World," Dr. Tankersley said.

"The ancient Maya lived in a tropical environment and had to be innovators. This is a remarkable innovation."

"A lot of people look at Native Americans in the western hemisphere as not having the same engineering or technological muscle of places like Greece, Rome, India or China. But when it comes to water management, the Maya were millennia ahead."

A paper on the findings was published in the journal *Scientific Reports*.

K.B. Tankersley et al. 2020. Zeolite water purification at Tikal, an ancient Maya city in Guatemala. Sci Rep 10, 18021; doi: 10.1038/s41598-020-75023-7

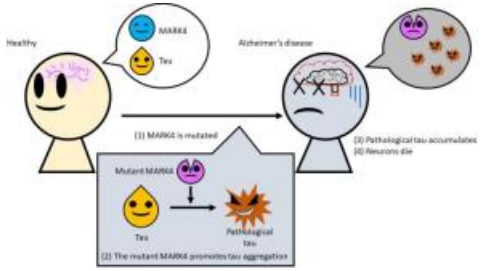
https://bit.ly/3knXT7b

Cause of Alzheimer's disease traced to mutation in common enzyme

Mutation to MARK4 makes proteins stickier and more likely to clump in brain

Tokyo, Japan - Researchers from Tokyo Metropolitan University have discovered a new mechanism by which clumps of tau protein are created in the brain, killing brain cells and causing Alzheimer's disease. A specific mutation to an enzyme called MARK4 changed the properties of tau, usually an important part of the skeletal structure of cells, making it more likely to aggregate, and more insoluble. Getting to grips with mechanisms like this may lead to breakthrough treatments.

Alzheimer's disease is a life-changing, debilitating condition, affecting tens of millions of people worldwide. According to the World Health Organization, it is the most common cause of senile dementia, with numbers worldwide expected to double every 20 years if left unchecked.



The mutant MARK4 creates a form of tau which accumulates easily in brain cells, causing neurons to die. **Tokyo Metropolitan University**

Alzheimer's is said to be caused by the build-up of tangled clumps of a protein called "tau" in brain cells. These sticky aggregates cause neurons to die, leading to impairment in memory and motor functions. It is not yet clear how and why tau builds up in the brain cells of Alzheimer's patients. Understanding the cause and mechanism behind this unwanted clumping would open up the way to new treatments and ways to prevent the disease.

A team led by Associate Professor Kanae Ando of Tokyo Metropolitan University has been exploring the role played by the MARK4 (Microtubule Affinity Regulating Kinase 4) enzyme in Alzheimer's disease. When everything is working normally, the tau protein is an important part of the structure of cells, or the cytoskeleton. To keep the arms of the cytoskeleton or *microtubules* constantly building and disassembling, MARK4 actually helps tau detach from the arms of this structure.

Problems start when a mutation occurs in the gene that provides the blueprint for making MARK4. Previous work had already

associated this with an increased risk of Alzheimer's, but it was not known why this was the case. The team artificially introduced mutations into transgenic *drosophila* fruit flies that also produce human tau, and studied how the proteins changed *in vivo*. They discovered that this mutant form of MARK4 makes changes to the tau protein, creating a pathological form of tau. Not only did this "bad" tau have an excess of certain chemical groups that caused it to misfold, they found that it aggregated much more easily and were no longer soluble in detergents. This made it easier for tau to form the tangled clumps that causes neurons to degenerate.

MARK4 has also been found to cause a wide range of other diseases which involve the aggregation and buildup of other proteins. That's why the team's insights into tau protein buildup may lead to new treatments and preventative measures for an even wider variety of neurodegenerative conditions.

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (Brain Protein Aging and Dementia Control) [JSPS KAKENHI Grant number 17H05703], a research award from the Hoan-sha Foundation, the Takeda Science Foundation, a research award from the Japan Foundation for Aging and Health, a Grant-in-Aid for Scientific Research on Challenging Research (Exploratory) [JSPS KAKENHI Grant number 19K21593], and Research Funding for Longevity Science 19-7 from the National Center for Geriatrics and Gerontology, Japan.

https://bit.ly/37Bq45P

Huge COVID study finds remdesivir doesn't work—FDA grants approval anyway

WHO says its massive study was clearly not included in FDA review.

Beth Mole

The US Food and Drug Administration on Thursday issued a full approval of the antiviral drug remdesivir for treating COVID-19—just days after a massive global study concluded that the drug provides no benefit.

"The FDA is committed to expediting the development and availability of COVID-19 treatments during this unprecedented public health emergency," FDA Commissioner Stephen Hahn said in a statement. "Today's approval is supported by data from multiple clinical trials that the agency has rigorously assessed and represents an important scientific milestone in the COVID-19 pandemic."

A vial of Remdesivir during a press conference about the start of a study with severely COVID-19 patients in Hamburg, Germany on April 8, 2020. Getty | Ulrich Perrey

Early results

The FDA made its decision based on three clinical trials on remdesivir, a repurposed experimental antiviral drug brand-named Veklury. One was a randomized, double-blind, placebo-controlled trial run by the National Institute of Allergy and Infectious Diseases. It included 1,062 hospitalized COVID-19 patients, 541 of which received remdesivir. The trial concluded that remdesivir shortened the median recovery time from the infection from 15 days to 10 days. The researchers running the trial defined "recovery" of a patient as either a patient being discharged from the hospital—regardless if the patient still had lingering symptoms that limited activities or required supplemental oxygen to be taken at home—or a patient remaining in the hospital but no longer requiring medical care, such as if they were kept in the hospital for infection-control reasons.

The other two trials the FDA considered were conducted by Gilead, the company that makes remdesivir. One trial looked at about 600 people with moderate cases COVID-19. Patients were split into three groups, each about 200 people—a group that got a 10-day course of remdesivir, a group that got a 5-day course, and a control

group that got standard treatments. At day 11 of treatments, the group that had the 5-day course of remdesivir showed a statistically significant improvement in symptom scores compared with the control group. The group that got a 10-day course of remdesivir did not have a statistically significant improvement over the control group, though.

The other Gilead trial looked at 400 patients with severe COVID-19. They were split about evenly into just two groups—a group that got a 5-day course of remdesivir and a group that got a 10-day course. There were no statistically significant differences in recovery or deaths between the two groups.

Missing data

"The [FDA] approval of Veklury marks an important milestone in efforts to help address the pandemic by offering an effective treatment that helps patients recover faster and, in turn, helps preserve scarce healthcare resources," Barry Zingman said in a press statement released by Gilead. Zingman is a professor at Albert Einstein College of Medicine and one of the researchers who conducted the NIAID trial of remdesivir.

But the FDA's approval of remdesivir falls on the heels of data form the fourth and largest trial of the drug, and that trial showed no benefit. The data comes from the World Health Organization's massive Solidarity trial, which set up an international network of trials enrolling nearly 12,000 patients at 500 sites in over 30 countries, testing multiple repurposed therapeutics. Remdesivir was initially developed over a decade ago as a potential treatment for hepatitis C and RSV (respiratory syncytial virus). It has also been tested against Ebola but was beat out by other treatments.

According to preliminary results from the Solidarity trial—reported online last week ahead of its planned publication in the New England Journal of Medicine—remdesivir was given to 2,743 patients, and their outcomes were compared with those of 2,708 patients given standard treatments. Between the two groups, WHO found that remdesivir did not reduce mortality. It also did not change how many patients progressed to needing mechanical ventilation, nor did it change the proportion of patients discharged after seven days of hospitalization.

When the Solidarity trial data was first released, Gilead blasted the results, saying, "The emerging data appear inconsistent with more robust evidence from multiple randomized, controlled studies validating the clinical benefit of [remdesivir]."

Can't fudge this

But in a press conference Friday, the WHO hit back, arguing that the data was, in fact, more robust that the smaller trials that came before it and should certainly be included in any regulatory or clinical decision.

"It is the largest trial in the world," WHO's chief scientist, Soumya Swaminathan noted. And unlike the NIAID study, which used a somewhat subjective clinical scoring system to compare disease progression and a range of definitions for "recovery," the Solidarity trial compared only clear, indisputable outcomes: mechanical ventilation, discharge from the hospital, and death.

"[Death is] not a soft end point," Swaminathan said. "You cannot fudge that endpoint."

Swaminathan also noted that it was clear that the FDA did not have the Solidarity trial data when it made its decision to approve remdesivir. But she emphasized that the WHO had provided that data to Gilead in advance. "They first saw the results on the 23rd of September," she said, well before it was made public. But "it appears the results were not considered—not provided to the FDA," she said.

Though the comments suggest the WHO doesn't support the FDA's decision to approve remdesivir for treating COVID-19, WHO experts also suggested that the FDA approval may be irrelevant.

Instead, expert clinical guidelines for treating patients are what matter most. “Regulatory authorities may place items on an approved list,” WHO Executive Director Michael Ryan said in the press conference. “That doesn’t necessarily mean that they will be used in any particular practice unless they pass into clinical guidance that’s given to doctors and nurses.”

The WHO noted that it is working on such clinical guidance and treatment recommendations and expects to release them in three to four weeks.

https://bit.ly/2TnM2tV

Naked Mole Rats Have Been Caught Kidnapping Other Mole Rat Babies, And It Gets Creepier

Highly social freaks of nature have a nasty little secret that makes them more supervillain than superhero

Tessa Koumoundouros

Naked mole rats are beloved for having some of the strangest mammalian superpowers. They can resist cancers, defy the usual mammalian ageing process, survive almost 20 minutes without oxygen, and tolerate surprisingly high levels of pain.

But it turns out these highly social freaks of nature have a nasty little secret that makes them more supervillain than superhero. Naked mole rats (*Heterocephalus glaber*) kidnap each other's babies and turn them into slaves.

Not as cute as you thought! **(Smithsonian's National Zoo/Flickr)**

While naked mole rats themselves are small, up to 10 cm (4 inches) in length, they have massive colonies made up of highly co-operative individuals. These can have up to a staggering 300 workers – the largest known colonies among mammals – within which most individuals are sterile, just like in ants or bee colonies.

In fact, these bucktoothed shrivelled skin sacks seem to be doing their darndest to live like insects.

Only one queen gets to reproduce, and she claims her throne through a murderous battle for dominance. She can give birth to up to 30 pups per litter and convinces subordinate female subjects to babysit by feeding them her hormone laced poop.

For a while, inbreeding was thought to play a role in the staggering size of naked mole rat colonies, based on results from early collections of the species. But this has since been shown unlikely.

In the early 1990s researchers caught and released naked mole rats to track them for a long-term field study in Kenya. They found 26 colonies expanded their burrows into neighbouring colonies. Individuals from 13 of the invaded colonies were never seen again.

A year after checking one of these colonies, they found two pups in an invading colony looked to have been from an invaded colony, but the team couldn't be sure it wasn't just a mistake.

"We just didn't have the tools to make sure that I hadn't totally screwed up," evolutionary biologist Stan Braude from Washington University told *New Scientist*. But genetic analysis of the tissues they collected has now confirmed what they witnessed.

"The pups kidnapped by colony QQ became non-reproductive workers," the team wrote in their paper, "hence their life effort would be categorized as slavery, in the same sense as slave-making ants."

Naked mole rat kidnapping behaviour had previously been witnessed in the unnatural conditions of a laboratory, but this is the first time it's been confirmed in the wild.

While kidnapping also occurs in some primate species, the team notes this behaviour is more like that seen in slave-making ants, such as *Formica sanguinea*. These insects hijack larvae and pupae of other species and raise them as part of their workforce.

This evolutionary phenomenon – where evolutionary pressure creates the same physical or behavioural features in entirely non-related species – is known as convergent evolution.

Pup snatching would certainly add to the mole-power required to find scarce resources in their harsh arid environment and help them construct their elaborate underground homes that can stretch for kilometres in cumulative tunnel length.

So much of their bizarre physiology helps with excavation, like jaw muscles that make a quarter of their mass and teeth that jut out over closed lips to keep them from swallowing dirt.

"The low probability of documenting this phenomenon with our mark-recapture methods, raises the possibility that this behaviour is far more common and may be a significant driver of sociality, and extreme large colony size, in naked mole-rats," Braude and colleagues explain.

If this is the case, the team believes fierce aggression between naked mole rat colonies may be driving the evolution of large group sizes, and slavery allows expanding colonies to increase their competitive advantage over neighbours.

However, that is still very much speculation at this point; they only found two stolen pups, after all. Braude and colleagues hope that new tracking technologies, like implantable transponders, will help sort out just how supervillainous these poop-eating freaklings are.

This research was published in the *Journal of Zoology*.

https://bit.ly/3dUHvsp

NASA Probe Has Collected a Bit Too Much Asteroid Dust And Is Now Leaking Its Treasure

NASA said Friday that its robotic spacecraft OSIRIS-REx had succeeded in collecting a large sample of particles from the Bennu asteroid this week – but so much that it was leaking.

The team in charge of the probe is now working to quickly stow the remaining samples that would eventually be delivered back to Earth to provide key scientific insights.

"A substantial fraction of the required collected mass is seen escaping," mission chief Dante Lauretta said in a phone briefing with journalists.

OSIRIS-REx is set to come home in September 2023, hopefully with the largest sample returned from space since the Apollo era, which will help unravel the origins of our solar system.

The probe is thought to have collected some 400 grams of fragments, far more than the minimum of 60 grams needed, Lauretta said.

But the lid for the collector at the end of the probe's arm where the fragments are being stored has been slightly wedged open by larger rocks, creating a leak, the scientists suspect.

Five to 10 grams have already been observed around the collection arm in a cloud remaining more or less in the surrounding area due to the microgravity environment, which makes fragments behave like fluids.

"My big concern now is that the particles are escaping because we were almost a victim of our own success here," Lauretta said.

As a result, a plan to carry out a mass measurement on Saturday has been cancelled since it could risk scattering further samples.

The task is now to reduce as much as possible the spacecraft's activities and prepare to stow the material in a capsule on the probe as quickly as possible.

Is OSIRIS-REx, launched more than four years ago, at risk of losing its treasure? The volume of the leak is not yet precisely known, but the experts seemed relatively confident that would not be the case.

"Bennu continues to surprise us with great science and also throwing a few curveballs," Thomas Zurbuchen, a NASA associate administrator, said in a statement.

"And although we may have to move more quickly to stow the sample, it's not a bad problem to have. We are so excited to see what appears to be an abundant sample that will inspire science for decades beyond this historic moment."