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Scientists 'program' living bacteria to store data

Escherichia coli bacteria can convert electrical pulses into bits of DNA stored in their genome.

By Robert F. Service

Hard disks and optical drives store gigabits of digital data at the press of a button. But those technologies—like the magnetic tapes and floppy drives before them—are apt to become antiquated and unreadable when they are overtaken by new technology. Now, researchers have come up with a way to electronically write data into the DNA of living bacteria, a storage option unlikely to go obsolete any time soon.

"This is a really nice step" that might one day spur commercial development, says Seth Shipman, a bioengineer at the Gladstone Institutes and the University of California, San Francisco, who was not involved in the new work. He notes, however, that real-world applications are a long way off.

DNA is attractive for data storage for several reasons. First, it is more than 1000 times as dense as the most compact hard drives, enabling it to store the equivalent of 10 full-length digital movies within the volume of a grain of salt. And because DNA is central to biology, the technologies to read and write it are expected to become cheaper and more powerful with time.

Storing data in DNA is not a new idea. To do so, researchers typically convert a data file's string of digital ones and zeros into combinations of the molecule's four bases: adenine, guanine, cytosine, and thymine. They then use a DNA synthesizer to write that code into DNA. But the accuracy of DNA synthesis decreases the longer the code gets, so researchers typically break their file into chunks and write those into snippets of DNA between 200 and 300 bases long. Each snippet is given an index to identify its location in the file, and DNA sequencers then read the snippets to reassemble the file. But the technology is expensive, costing up to $3500 to synthesize 1 megabit of information. And the vials of DNA in which information is stored can degrade over time.

To create a long-lasting, easier to encode medium, researchers are now working to write data into the DNA of living organisms, which copy and pass their genes on to the next generation. In 2017, a team led by Harris Wang, a systems biologist at Columbia University, used the CRISPR gene-editing system to recognize a biological signal, such as the presence of the sugar fructose. When researchers added fructose to *Escherichia coli* cells, gene expression increased in bits of ring-shaped DNA called plasmids.

Next, CRISPR components—which evolved to defend bacteria from viral invaders—chopped the overexpressing plasmid into pieces and lodged some of it into a specific section of the bacteria's DNA that "remembers" previous viral invaders. The inserted genetic bit represented a digital one. If the fructose signal was absent, the bacteria instead stored a random bit of DNA, representing a digital zero. Sequencing the *E. coli* DNA then revealed whether the bacteria was exposed to fructose, via a one or zero.

But because this setup could store only a couple of bits of data, Wang and his colleagues replaced the fructose-recognition system with one that could encode longer strings of information: an electronic input. They inserted a series of genes into *E. coli* that enabled the cells to increase plasmid expression in response to an electric voltage. As with the fructose setup, an increase in expression caused the digital one to be stored in the bacteria's DNA. To read out the ones and zeros, the researchers simply sequenced the bacteria.

Using this approach, Wang and his colleagues electrically encoded up to 72 bits of data, to write the message "Hello world!" they report today in *Nature Chemical Biology*. They also showed that

they could add *E. coli* with their message to a mix of normal soil microbes—and later sequence the mix to recover their stored message.

Wang says it is still early days for the storage of data in living organisms. “We’re not going to compete with the current memory storage systems,” he says. The researchers will also need to come up with ways to prevent their messages from degrading as the bacteria mutate as they replicate. But at least for now, it may give James Bond a new tool for hiding messages in plain sight.

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Sleep evolved before brains did, study finds

The researchers identified a sleep-like state in a tiny, brainless animal called a hydra.

By Rachael Rettner - Senior Writer

Our brains need sleep to work properly. But it turns out you don't need a brain to sleep.

Despite lacking a brain, Hydra vulgaris, shown above, still needs to sleep. **© Taichi Q. Itoh, Kyushu University**

In a new study, researchers identified a sleep-like state in a tiny, freshwater animal called a hydra, which has a simple anatomy and lacks a brain. "We now have strong evidence that animals must have acquired the need to sleep before acquiring a brain," study lead author Taichi Q. Itoh, an assistant professor at Kyushu University in Japan, said in a statement. The study, recently published in the journal Science Advances, has implications for our understanding of the reason the need for zzzs evolved.

Sleep is near universal in the animal kingdom, seen in humans and all mammals, as well as in insects and even roundworms. However, all these creatures have some form of central nervous system, or brain, and so scientists didn't know whether the evolution of sleep preceded that of brains, or vice versa.

Jellyfish, a relative of hydras that also lack a brain, have also demonstrated sleeplike behavior, Live Science previously reported. But the new study adds to these findings by showing that hydras not only sleep but also respond to the same molecules that regulate sleep in humans and other advanced animals.

"Based on our findings and previous reports regarding jellyfish, we can say that sleep evolution is independent of brain evolution," Itoh said.

For the study, the researchers used a video-recording system — essentially a "hydra cam" — to monitor the hydras' movement and determine whether they had entered a sleeplike state, or a state of reduced movement that could be disrupted with a flashlight.

They found that hydras had cycles of active and sleep states that lasted about four hours each. What's more, disrupting the hydras' sleep state, with vibrations or temperature changes, resulted in signs of sleep deprivation — for example, the hydras needed to sleep longer afterwards, and showed reduced cell growth.

The researchers also exposed the hydras to chemicals involved in sleep regulation in people, including melatonin and the neurotransmitter, or brain chemical called GABA. Exposure to both of these chemicals increased sleep activity in the hydras.

However, the chemical dopamine, which has a stimulating effect on many animals, instead promoted sleep in hydras. It seems that "while some sleep mechanisms appear to have been conserved, others may have switched function during evolution of the brain," Itoh said.

The authors also found that when they deprived the hydras of their "shuteye," there were changes in the expression of more than 200 genes, including some that are involved in sleep regulation in other animals. Overall, "these experiments provide strong evidence that animals acquired sleep-related mechanisms before the evolutional development of the central nervous system and that many of these mechanisms were conserved as brains evolved," Itoh said.

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The three days pregnancy sickness is most likely to start pinpointed

Researchers from the University of Warwick have narrowed the time frame that nausea and vomiting during pregnancy will potentially start to just three days for most women, opening up the possibility for scientists to identify a biological cause.

Researchers from the University of Warwick have narrowed the time frame that nausea and vomiting during pregnancy will potentially start to just three days for most women, opening up the possibility for scientists to identify a biological cause for the condition.

By measuring the onset of symptoms from a woman's date of ovulation for the first time, rather than last menstrual period, they have demonstrated that symptoms start earlier in pregnancy than previously thought, and within a smaller time frame.

Nausea and vomiting in pregnancy, often referred to as pregnancy sickness, which usually ends by 12 -14 weeks of pregnancy is experienced by most women during pregnancy although some will experience it more severely, as in the case of hyperemesis gravidarm when the symptoms can continue throughout the pregnancy. The cause has historically often been seen as psychological but this latest study reinforces the view that the cause is biological and is linked to a specific developmental stage of pregnancy.

Researchers from Warwick Medical School and the Department of Statistics at the University of Warwick have drawn their conclusions from a unique dataset collected at the Clearblue Innovation Centre, by SPD Development Company Ltd. Their results, published in the journal *BMC Pregnancy and Childbirth*, identify a specific time period during pregnancy that could point scientists to an anatomical or biochemical cause for the condition.

The date of a woman's last menstrual period is commonly used to measure the start of pregnancy, but their date of ovulation is thought to be a more accurate starting point as menstrual cycles can vary greatly between individuals, and even between cycles for the same individual.

The researchers used data from daily symptom diaries kept by 256 pregnant women to compare the start of their nausea and vomiting symptoms to the date of their last menstrual period and date of ovulation, as determined by a urine test.

Using their date of ovulation as the start of pregnancy most women experienced the first symptoms of pregnancy sickness after 8 to 10 days, compared to 20 to 30 days if measured from their last menstrual period. This not only demonstrated that pregnancy sickness starts earlier than previous research has shown, but has also shown that using date of ovulation narrows the time frame that symptoms start to 3 days, compared to 11 days if last menstrual period is used.

Lead author Professor Roger Gadsby of Warwick Medical School said: "The precise course of pregnancy sickness is unknown, but this research shows that it occurs at a specific developmental stage, in a specific timeslot.

"For researchers it narrows our focus in terms of where we look for the cause. If we know that symptoms occur in a very narrow window 8-10 days after ovulation, researchers can concentrate their efforts on that particular stage of development to find the cause of the condition, both anatomically and biochemically.

"In the past, women suffering with nausea and vomiting in pregnancy have had their symptoms trivialised and overlooked because it was thought there was a psychological basis for the symptoms. This research further reinforces that nothing could be further from the truth, that this is a biological problem related to the development of the early fetus."

The research also found that 94% of women experienced symptoms of pregnancy sickness, a higher proportion than previous research that generally calculates the proportion as closer to 80%. This is likely to be because data was regularly collected from participants before they became pregnant up to 60 days after last menstrual period, while most other studies ask women to recall their symptoms after they have become pregnant.

Professor Roger Gadsby adds: "What we've shown is that more people get symptoms of pregnancy sickness than has ever been shown before, and one of the reasons for that is that this research has picked up mild early symptoms that tend to fade by 7-8 weeks. In other studies those symptoms would have faded by the time the research started."

Previous research by the same team has demonstrated that the term 'morning sickness' is misleading as nausea and vomiting can occur at any time of day, and argues that 'nausea and sickness in pregnancy' or 'pregnancy sickness' is more appropriate and avoids trivialising the condition.

'The onset of nausea and vomiting of pregnancy: a prospective cohort study' is published in BMC Pregnancy and Childbirth, DOI: 10.1186/s12884-020-03478-7 Link: https://doi.org/10.1186/s12884-020-03478-7

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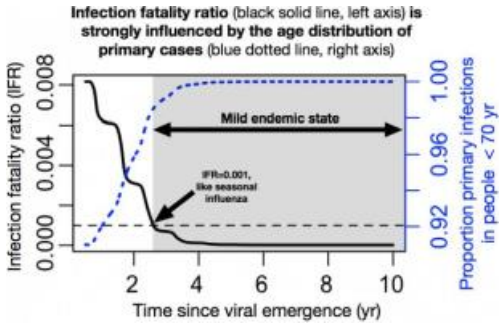
Another common cold virus? Modeling SARS-CoV-2's progress through the ages

Model predicts transition to endemic and mild

What is the endgame for SARS-CoV-2, the virus that is causing worldwide devastation? If it becomes endemic -- circulating in the general population -- and most people are exposed in childhood, SARS-CoV-2 may join the ranks of mild cold-causing coronaviruses that currently circulate in humans, according to a model developed by Emory and Penn State scientists.

The model, published January 12 in *Science*, draws upon studies of the four common cold coronaviruses and SARS-CoV-1. For those viruses, the term "herd immunity" is incomplete and possibly misleading, says postdoctoral fellow Jennie Lavine, PhD, first author of the *Science* paper.



Simulation shown with R0=4. Faster transmission results in a quicker transition to the endemic state but more total deaths. Social distancing saves lives, delays endemicity and allows crucial time for vaccine roll-out. Vaccination speeds up the transition to the endemic state and reduces the death toll. **Credit: Jennie Lavine**

The four common cold-causing coronaviruses have been circulating in humans for a long time and almost everyone is infected at a young age - younger than measles before a vaccine was available. Natural infection in childhood provides immunity that protects people later in life against severe disease, but it doesn't prevent periodic reinfection, says Lavine.

"Reinfection is possible within one year, but even if it occurs, symptoms are mild and the virus is cleared from the body more quickly," she says. "It highlights the need to tease apart the components of immunity to SARS-CoV-2. How long does immunity that prevents pathology last, and how long does immunity that prevents transmission last? Those durations may be very different."

Studies are now emerging that provide concrete data on how long antibodies and immune cells against SARS-CoV-2 last after infection, Lavine says. However, researchers are still figuring out how those components translate to protection against disease or transmission.

"Overall, we're asking: how does SARS-CoV-2 compare to other viruses such as seasonal influenza or respiratory syncytial virus,"

she says. "This model assumes immunity to SARS-CoV-2 works similar to other human coronaviruses. We don't really know what it would be like if someone got one of the other coronaviruses for the first time as an adult, rather than as a child."

The model predicts that the infection fatality ratio for SARS-CoV-2 may fall below that of seasonal influenza (0.1 percent), once an endemic steady-state is reached.

"We are in uncharted territory, but a key take-home message from the study is that immunological indicators suggest that fatality rates and the critical need for broad-scale vaccination may wane in the near term, so maximum effort should be on weathering this virgin pandemic enroute to endemicity," said Ottar Bjornstad, Distinguished Professor of Entomology and Biology and J. Lloyd & Dorothy Foehr Huck Chair of Epidemiology, Penn State.

Lavine developed the model, together with Bjornstad and Rustom Antia, PhD, Samuel C. Dobbs professor of biology at Emory University and Emory Vaccine Center.

A safe and effective vaccine against COVID-19 could save hundreds of thousands of lives in the first year or two of vaccine roll-out, but continued mass vaccination may be less critical once SARS-CoV-2 becomes endemic, the authors say. Targeted vaccination in vulnerable subpopulations may still save lives, they say.

Another implication is: during the transition to endemicity, that using symptoms only as a surveillance tool to look for infections and curb the virus' spread will become more difficult. Thus, widely available testing may become particularly important during vaccine roll-out to protect vulnerable populations, the authors point out.

So far, the available data on SARS-CoV-2 infection in infants and young children suggest that severity is generally mild and mortality is low. There are exceptions on the individual level, with some experiencing rare complications such as MIS-C (multisystem inflammatory syndrome in children). In contrast, if SARS-CoV-2 infection in childhood were to become more severe - like MERS-CoV (Middle East respiratory syndrome-related coronavirus) - routine vaccination programs will be still necessary, the authors say.

The research was supported by the National Institute of Allergy and Infectious Diseases (U01 AI150747, U01AI144616) and the National Heart Lung and Blood Institute (U01HL139483).

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Computer scientists: We wouldn't be able to control super intelligent machines

New findings from theoretical computer science

We are fascinated by machines that can control cars, compose symphonies, or defeat people at chess, Go, or Jeopardy! While more progress is being made all the time in Artificial Intelligence (AI), some scientists and philosophers warn of the dangers of an uncontrollable superintelligent AI. Using theoretical calculations, an international team of researchers, including scientists from the Center for Humans and Machines at the Max Planck Institute for Human Development, shows that it would not be possible to control a superintelligent AI. The study was published in the *Journal of Artificial Intelligence Research*.

Suppose someone were to program an AI system with intelligence superior to that of humans, so it could learn independently. Connected to the Internet, the AI may have access to all the data of humanity. It could replace all existing programs and take control all machines online worldwide. Would this produce a utopia or a dystopia? Would the AI cure cancer, bring about world peace, and prevent a climate disaster? Or would it destroy humanity and take over the Earth?

Computer scientists and philosophers have asked themselves whether we would even be able to control a superintelligent AI at all, to ensure it would not pose a threat to humanity. An

international team of computer scientists used theoretical calculations to show that it would be fundamentally impossible to control a super-intelligent AI.

"A super-intelligent machine that controls the world sounds like science fiction. But there are already machines that perform certain important tasks independently without programmers fully understanding how they learned it. The question therefore arises whether this could at some point become uncontrollable and dangerous for humanity", says study co-author Manuel Cebrian, Leader of the Digital Mobilization Group at the Center for Humans and Machines, Max Planck Institute for Human Development.

Scientists have explored two different ideas for how a superintelligent AI could be controlled. On one hand, the capabilities of superintelligent AI could be specifically limited, for example, by walling it off from the Internet and all other technical devices so it could have no contact with the outside world -- yet this would render the superintelligent AI significantly less powerful, less able to answer humanities quests. Lacking that option, the AI could be motivated from the outset to pursue only goals that are in the best interests of humanity, for example by programming ethical principles into it. However, the researchers also show that these and other contemporary and historical ideas for controlling super-intelligent AI have their limits.

In their study, the team conceived a theoretical containment algorithm that ensures a superintelligent AI cannot harm people under any circumstances, by simulating the behavior of the AI first and halting it if considered harmful. But careful analysis shows that in our current paradigm of computing, such algorithm cannot be built.

"If you break the problem down to basic rules from theoretical computer science, it turns out that an algorithm that would command an AI not to destroy the world could inadvertently halt its own operations. If this happened, you would not know whether the containment algorithm is still analyzing the threat, or whether it has stopped to contain the harmful AI. In effect, this makes the containment algorithm unusable", says Iyad Rahwan, Director of the Center for Humans and Machines.

Based on these calculations the containment problem is incomputable, i.e. no single algorithm can find a solution for determining whether an AI would produce harm to the world. Furthermore, the researchers demonstrate that we may not even know when superintelligent machines have arrived, because deciding whether a machine exhibits intelligence superior to humans is in the same realm as the containment problem.

The study "Superintelligence cannot be contained: Lessons from Computability Theory" was published in the Journal of Artificial Intelligence Research. Other researchers on the study include Andres Abeliuk from the University of Southern California, Manuel Alfonseca from the Autonomous University of Madrid, Antonio Fernandez Anta from the IMDEA Networks Institute and Lorenzo Coviello.

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Evolution in a test tube: these bacteria survive on deadly copper surfaces

The descendants of regular wild-type bacteria can evolve to survive for a long time on metallic copper surfaces that would usually kill them within a few minutes.

An international research team led by Martin Luther University Halle-Wittenberg (MLU) and the Bundeswehr Institute of Microbiology was able to produce these tiny survivalists in the lab and has been able to study them more closely. The team reports on its findings in *Applied and Environmental Microbiology*.

Bacterial infections are usually treated with antibiotics. However, in recent decades many pathogenic bacteria have developed an increasing tolerance to common drugs. So-called multidrug-resistant bacteria are of particular concern as they can no longer be combated with most antibiotics. Copper surfaces - for example on

door handles - are a good weapon to fight these germs. "Copper surfaces are a sure-fire way to kill bacteria. Most bacteria die within minutes after landing on a copper surface," explains Professor Dietrich H. Nies, a microbiologist at MLU. Copper is a vital trace element for bacteria - but only in very small quantities. On the copper surfaces, however, the bacteria are literally flooded to death with copper ions because that they can no longer stave them off using their normal defence strategies.

Nies' research team wanted to find out if and how quickly two typical species of bacteria, Escherichia coli and Staphylococcus aureus, are theoretically able to adapt to survive on copper surfaces. The team therefore placed the bacteria on the surfaces for only a few minutes before returning them to a normal culture medium where they were allowed to recover. This process was repeated several times, with the survivors gradually being exposed to the deadly surface for longer and longer periods of time. Within three weeks, the researchers had produced bacteria that could survive for more than one hour on a copper surface. "Outside the laboratory, conditions are obviously not as ideal. But if copper surfaces are not cleaned regularly, insulating layers of grease can begin to form on them, which could produce a similar development over time," says Nies.

Using comprehensive genetic analyses, the team sought to understand why the bacteria no longer died on the surfaces. "We were unable to find a gene that made them resistant to the deadly effect of metallic copper surfaces," says Nies. Instead, the team observed a phenomenon among the surviving bacteria that was already known for quite some time, although in a slightly different manner: the bacteria's metabolism slowed down to a bare minimum and they fell into a kind of hibernation. Because most antibiotics aim to disrupt the metabolism of growing bacteria, they are almost completely ineffective against these special bacteria, which are also known as "persisters". "No matter how well an antibiotic works, there are always a handful of persisters in every generation," explains Nies. However, these are not considered antibiotic-resistant bacteria, because their offspring are once again susceptible to the drugs.

Normally only a tiny proportion of bacteria become persisters. However, in the case of the isolated bacteria, it was the entire population. Although they were able to grow just as fast as their predecessors, they were also able to rescue themselves by switching rapidly into an early state of persistence under adverse conditions. The scientists were concerned one additional thing they observed: "The bacteria also inherited this capability over 250 generations, even though the offspring had not come into contact with a copper surface," says Nies. The team therefore recommends that copper surfaces be cleaned regularly and thoroughly with special agents so that no persister bacteria can develop in the first place. At the same time, Nies points out that the use of copper surfaces is only one of many ways - including antibiotics - to effectively combat harmful bacteria.

Bleichert et al. Generation and analysis of mutant strains of Escherichia coli and methicillin-resistant Staphylococcus aureus obtained by laboratory selection to survive on metallic copper surfaces. Applied and Environmental Microbiology (2021). Doi: 10.1128/AEM.01788-20

http://bit.ly/2Ko6s5e

Dire Wolves Were Not Really Wolves, New Genetic Clues Reveal

The extinct giant canids were a remarkable example of convergent evolution

By Riley Black

Dire wolves are iconic beasts. Thousands of these extinct Pleistocene carnivores have been recovered from the La Brea Tar Pits in Los Angeles. And the massive canids have even received some time in the spotlight thanks to the television series *Game of*

Thrones. But a new study of dire wolf genetics has startled paleontologists: it found that these animals were not wolves at all, but rather the last of a dog lineage that evolved in North America.

Ever since they were first described in the 1850s, dire wolves have captured modern humans' imagination. Their remains have been found throughout much of the Americas, from Idaho to Bolivia. The La Brea asphalt seeps famously document how prey animals mired in tar lured many of these ice age predators to a sticky death. The dire wolves' tar-preserved remains reveal an imposing hunter up to six feet long, with skull and jaw adaptations to take down enormous, struggling megafauna. Though these canids had clearly evolved to handle the mastodons, horses, bison and other large herbivores then roaming the Americas, skeletal resemblances between dire wolves and the smaller gray wolves of today suggested a close kinship.

It had long been assumed that dire wolves made themselves at home in North America before gray wolves followed them across the Bering Land Bridge from Eurasia. Now some well-preserved DNA seems to be fundamentally changing the story.

Somewhere in southwestern North America during the late Pleistocene, a pack of dire wolves (Canis dirus) are feeding on their bison kill while a pair of gray wolves (Canis lupus) approach in the hopes of scavenging. One of the dire wolves rushes in to confront the gray wolves, and their confrontation allows a comparison of the bigger, larger-headed and reddish-brown dire wolf with its smaller gray relative. **Credit: Mauricio Antón**

The new study, published on Wednesday in *Nature*, began as an effort to understand dire wolves' biological basics. "For me, it started with a decision to road-trip around the U.S. collecting dire wolf samples and see what we could get, since no one had managed to get DNA out of dire wolf samples at that point," says Durham University archaeologist and study co-author Angela Perri. At the same time, geneticist and co-author Kieren Mitchell of the University of Adelaide in Australia was also trying to extract and study ancient DNA from dire wolf remains—as were other labs that eventually collaborated on the project.

One of the researchers' questions was how dire wolves were related to other wolves. For decades, paleontologists have remarked on how similar the bones of dire wolves and gray wolves are. Sometimes it is difficult to tell them apart. "My hunch was that dire wolves were possibly a specialized lineage or subspecies of gray wolf," Mitchell says.

But the new evidence told a different story. Preliminary genetic analyses indicated that dire and gray wolves were *not* close relatives. "I think I can speak for the whole group when I say the results were definitely a surprise," Perri says.

After sequencing five genomes from dire wolf fossils between 50,000 and 13,000 years old, the researchers found that the animals belonged to a much older lineage of dogs. Dire wolves, it now appeared, had evolved in the Americas and had no close kinship with the gray wolves from Eurasia; the last time gray wolves and dire wolves shared a common ancestor was about 5.7 million years ago. The strong resemblance between the two, the researchers say, is a case of convergent evolution, whereby different species develop similar adaptations—or even appearances—thanks to a similar way of life. Sometimes such convergence is only rough, such as both birds and bats evolving wings despite their differing anatomy. In the case of dire and gray wolves, lives of chasing large herbivores to catch some meat on the hoof resulted in two different canid lineages independently producing wolflike forms.

"These results totally shake up the idea that dire wolves were just bigger cousins of gray wolves," says Yukon paleontologist Grant

Zazula, who was not involved in the new study. In fact, the similarity between the two has led gray wolves to be taken as proxies for dire wolf biology and behavior, from pack dynamics to the sound of the animal's howls. The dire wolf's new identity means that many previous assumptions—down to what it looked like in life—require reinvestigation. "The study of ancient DNA and proteins from fossil bones is rapidly rewriting the ice age and more recent history of North America's mammals," Zazula says.

In technical terms, the new findings mean dire wolves may need a new genus name to indicate they are no longer be part of the genus *Canis*, to which gray wolves belong. Perri, Mitchell and their colleagues suggest *Aenocyon*, meaning "terrible wolf." But the researchers don't expect their findings to completely overturn tradition, and *Aenocyon dirus* would likely continue to be called the dire wolf. "They will just join the club of things like maned wolves that are called wolves but aren't really," Perri says.

The new findings also add layers to experts' ruminations on why dire wolves eventually disappeared as the last ice age closed. These predators became specialized in hunting camels, horses, bison and other herbivores in North America over millions of years. As those prey sources disappeared, so did the dire wolves. "In contrast to gray wolves, which are a model for adaptation," Perri says, "dire wolves appear to be much less flexible to deal with changing environments and prey."

Nor did dire wolves leave a genetic legacy beyond the decaying DNA in their ancient bones. Although canids such as wolves and coyotes often create hybrids, dire wolves apparently did not do so with any other canids that remain alive today. Perri, Mitchell and their colleagues found no DNA evidence of interbreeding between dire wolves and gray wolves or coyotes. Dire wolves were genetically isolated from other canids, Mitchell notes, so "hybridization couldn't provide a way out" because dire wolves were probably unable to produce viable offspring with the recently arrived wolves from Eurasia.

By 13,000 years ago, dire wolves were facing extinction. Evolving in the harsh, variable environments of Eurasia may have given gray wolves an edge, Zazula notes, "while the big, bad dire wolves got caught off guard relaxing in southern California at the end of the ice age." But what might sound like the end of the dire wolf's story is really only the beginning. Preserved genes have shown that dire wolves and their ancestors were top dogs in the Americas for more than five million years—and the early chapters of their story are waiting to be rewritten.

http://bit.ly/2LWRZ0A

The cancer microbiome reveals which bacteria live in tumors

Researchers clean up data to identify the bugs better

Durham, N.C. -- Biomedical engineers at Duke University have devised an algorithm to remove contaminated microbial genetic information from The Cancer Genome Atlas (TCGA). With a clearer picture of the microbiota living in various organs in both healthy and cancerous states, researchers will now be able to find new biomarkers of disease and better understand how numerous cancers affect the human body.

In the first study using the newly decontaminated dataset, the researchers have already discovered that normal and cancerous organ tissues have a slightly different microbiota composition, that bacteria from these diseased sites can enter the bloodstream, and that this bacterial information could help diagnose cancer and predict patient outcomes. The results appear online on December 30 in the journal *Cell Host & Microbe*.

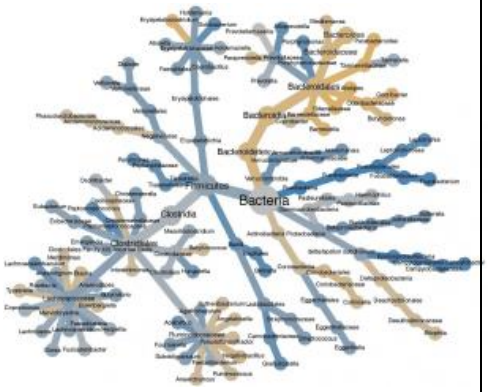
TCGA is a landmark cancer genomics program that molecularly characterized over 20,000 primary cancer and matched healthy samples spanning 33 cancer types. It has produced more than 2.5

million gigabytes of "omic" data. The atlas includes which DNA is present, what epigenetic markers are on the DNA, which DNA is turned on and which proteins are being produced. It is freely available for public use.

One study from the atlas data revealed an abundance of Fusobacterium nucleatum in colorectal cancer, which has since been shown to be indicative of stage, survival, metastasis and even drug responses of this kind of cancer. Many more studies have searched for such bacterial biomarkers, however few have been discovered. A large reason for this is contamination. When bacteria get introduced into the samples accidentally by the laboratories, it becomes difficult to discern which species were actually in the samples to begin with.

While similar microbiome studies using microbe-rich material such as feces can overcome small amounts of contamination, the relatively miniscule samples taken from live human organs and tumor samples cannot.

When examining a subset of TCGA sequencing data, previous analyses found that microbial DNA from a number of species was the result of lab contamination.



A diagram of the species of bacteria from an individual patient that are more likely to be found with tumor samples (blue) or normal tissue samples (yellow). The layout of the diagram shows the bacterial family tree, with node sizes proportional to the number of times a given bacterial group is observed. This specific diagram "rediscovers" that Fusobacterium species are strongly enriched in colorectal cancer and offers the new insight that Campylobacter species are also associated with the disease. **Anders Dohlman, Duke University**

"All microbiota studies are plagued by the notion that if you find a microbe, was it really in the tissue or was it contamination introduced during processing?" said Xiling Shen, the Hawkins Family Associate Professor of Biomedical Engineering at Duke. "We've invented a method that can extract the microbes that were truly in each sample and used it to build what we've called The Cancer Microbiome Atlas, which will be a tremendous resource for the community and allow us to understand how cancer alters an organ's microbiome."

The method for removing contamination from TCGA data was invented by Anders Dohlman, a graduate student in Shen's laboratory. Dohlman first compared the microbiome signatures between cancer tissues from different organs and blood, and ruled out contaminant species that showed up indiscriminately. He then compared the microbiome signatures of identical samples that were processed at separate sites, ranging from Harvard to Baylor. Dohlman concluded that the microbial species that can only be detected from a specific site would be the contaminants, allowing him to assign a unique contamination signature for each site.

"A big challenge in this process was mixed-evidence species, which are bacteria that are both a contaminant and endogenous to the tissue," said Dohlman. "But because TCGA has so many different types of data, we were able to tease it out. Big data really helps!"

The effort is already paying dividends in a variety of ways. After using Dohlman's decontamination algorithm, the researchers took a close look at the microbiota signatures of samples taken from colorectal cancer patients. They discovered two unique groups of bacteria frequently found together, one of which appears to be associated with patient survival.

The researchers also discovered that some cancers do indeed alter the microbiome of their resident organs. It might be, Shen reasons, that tumors alter an organ's microenvironment, making it more or less hospitable to different microbial species. And by looking for microbial signatures within patient blood samples, they also found

that, despite conventional wisdom to the contrary, some bacteria does find its way into the bloodstream, which could also provide an indication of a cancer's progress.

"There has been a sort of crisis in the field about whether or not high-profile papers can be reproduced, owing to the challenge of contamination," said Shen. "For example, while one center would be able to reproduce its results, another center would not. This explains why: Each center has its own very consistent bias. (Its own resident microbe contaminants.) In the future, new studies can use our method to remove this bias and reproduce results, and research centers might be able to use their bias we've identified to mitigate their contamination."

This research was supported by the National Institutes of Health (R35GM122465, DK119795) and the Defense Advanced Research Projects Agency (W911NF1920111).
CITATION: "The Cancer Microbiome Atlas: A Pan-Cancer Comparative Analysis to Distinguish Tissue-Resident Microbiota from Contaminants." Anders B. Dohlman, Diana Arguijo Mendoza, Shengli Ding, Michael Gao, Holly Dressman, Iliyan D. Iliev, Steven M. Lipkin, Xiling Shen. Cell Host & Microbe, 2021. DOI: 10.1016/j.chom.2020.12.001

http://bit.ly/2Kj4ov8

Compound from medicinal herb kills brain-eating amoebae in lab studies

Leaves from Inula viscosa, a Mediterranean perennial shrub, contain a compound that kills brain-eating amoebae.

Primary amoebic meningoencephalitis (PAM), a deadly disease caused by the "brain-eating amoeba" *Naegleria fowleri*, is becoming more common in some areas of the world, and it has no effective treatment.

Now, researchers reporting in *ACS Chemical Neuroscience* have found that a compound isolated from the leaves of a traditional medicinal plant, *Inula viscosa* or "false yellowhead," kills the amoebae by causing them to commit cell suicide in lab studies, which could lead to new treatments.

PAM, characterized by headache, fever, vomiting, hallucinations and seizures, is almost always fatal within a couple of weeks of developing symptoms.

Although the disease, which is usually contracted by swimming in contaminated freshwater, is rare, increasing cases have been reported recently in the U.S., the Philippines, southern Brazil and some Asian countries.

Amphotericin B is the most common therapy given to those with the infection.

It can kill *N. fowleri* in the lab, but it isn't very effective when given to patients, likely because it cannot cross the blood-brain barrier.

Ikrame Zeouk, José Piñero, Jacob Lorenzo-Morales and colleagues wanted to explore whether compounds isolated from *I. viscosa*, a strong-smelling plant that has long been used for traditional medicine in the Mediterranean region, could effectively treat PAM.

The researchers first made an ethanol extract from the herb's leaves, finding that it could kill *N. fowleri* amoebae.

Then, they isolated and tested specific compounds from the extract.

The most potent compound, inuloxin A, killed amoebae in the lab by disrupting membranes and causing mitochondrial changes, chromatin condensation and oxidative damage, ultimately forcing the parasites to undergo programmed cell death, or apoptosis.

Although inuloxin A was much less potent than amphotericin B in the lab, the structure of the plant-derived compound suggests that it might be better able to cross the blood-brain barrier. More studies are needed to confirm this hypothesis, the researchers say.

More information: *Ikrame Zeouk et al. Exploring the Anti-Infective Value of Inuloxin A Isolated from Inula viscosa against the Brain-Eating Amoeba (Naegleria fowleri) by Activation of Programmed Cell Death, ACS Chemical Neuroscience (2020). DOI: 10.1021/acschemneuro.0c00685*

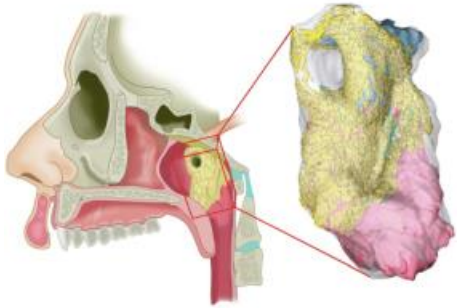
http://bit.ly/2LvkRxa

Scientists Question Discovery of New Human Salivary Gland

A widely publicized paper has drawn scrutiny from physicians and anatomists about the authors' claims regarding so-called tubarial glands.

Diana Kwon

Last year, a paper reporting the discovery of a pair of salivary glands made headlines at numerous publications, including *The Scientist*. That manuscript, which was published in *Radiotherapy & Oncology*, has since received criticism from several groups of scientists who question the authors' claims. To date, at least eight letters to the editor have been submitted to the journal in response to the paper.



ABOVE: A 3-D reconstruction from histological slides (inset on right) of the newly discovered tubarial gland (yellow; ducts in light blue). The torus tubarius cartilage is colored dark blue and muscle is pink. **M. Valstar et al., Radiotherapy & Oncology, doi:10.1016/j.radonc.2020.09.034, 2020.**

"I don't think the paper should be retracted, it should just be corrected," says Daniel Cohen Goldemberg, an oral pathologist at the National Cancer Institute of Brazil and an author of one of the letters. "It's a good paper, it's just not focusing on what it should be."

In the paper, a group of researchers from the Netherlands describe a pair of salivary glands dubbed "tubarial glands" for their location in the torus tubarius, a section in the nasopharynx—the upper portion of the throat. These findings were based on the team's examinations of scans from 100 cancer patients, dissections of two human cadavers, and imaging in one healthy volunteer. After finding that exposure to radiotherapy was associated with dry mouth and swallowing difficulties in a previously collected dataset of more than 700 head and neck cancer patients, they noted that these glands may be at risk for damage from this treatment.

Multiple issues were raised in the letters sent to the journal, but one of the most common included questions about the novelty of the Dutch team's finding. One letter pointed out, for example, that the existence of a structure fitting the description of the tubarial glands has been around since the 19th century. Others questioned whether it was appropriate to classify this structure as a salivary gland at all. Some scientists noted that due to issues such as the location of the glands, which suggests that their fluids do not reach the mouth and that they are therefore not involved in the production of saliva, and the glands' apparent lack of amylase, a key protein found in saliva, it was not appropriate to classify the tubarial glands as salivary glands.

"The study would have been better if it had focused on the [importance for radiotherapy] instead of trying to create this supposed new gland, because there is no new gland," says Cohen Goldemberg. "If I had been a reviewer [of the paper], I would probably not have rejected it, but I would surely not accept it as-is."

In another letter, the authors pointed out all but one of the 100 patients in the sample used to identify the tubarial glands were male. Because of this gender imbalance, the authors note that it will be important to conduct further analyses to determine if are any differences in these structures in females.

Reports of new discoveries in human anatomy are rare—and often fraught with debate. Other recent claims of previously unknown bits of human anatomy, such as the mesentery, a fan-like sheet of tissue holding the intestines together, and the interstitium, a network of fluid-filled spaces between cells, have also been

questioned.

Albert Mudry, an otorhinolaryngology specialist and adjunct professor at Stanford University who coauthored one the letters in response to the tubarial glands paper, says that he is skeptical about any paper that claims to have discovered something completely novel—whether that's a new organ or a new scientific technique—because authors often fail to conduct a thorough scan of past literature to verify the novelty. The authors of the tubarial glands paper "use a different anatomical term, but [the structure] was already described many years before and many times before." Mudry's letter points out that in the 19th century, anatomists Jean Cruveilhier and Jakob Henle and otologist Adam Politzer described glands in this region of the throat.

The authors stand by their claims. In a response letter, they comment on the criticisms, stating, among other things, that evidence from their study does not rule out the possibly that fluids from the tubarial glands reach the mouth or that amylase is present. They also note that while there have been descriptions of such structures in the past, their study provides a new perspective on prior observations.

"We've conducted an extensive study, but obviously there are a lot of ways you can see it, or things that we missed," says Matthijs Valstar, an oral and maxillofacial surgeon at the Netherlands Cancer Institute (NKI) and a coauthor of the original study. He adds that there were a number of nuances about the findings mentioned in the paper—such as the acknowledgement that there might be disagreement about whether the tubarial glands were major or minor glands and whether they could be considered separate organs—that he thinks some of the letters did not acknowledge.

Wouter Vogel, a radiation oncologist at the NKI and another coauthor of the tubarial gland study, says he and his colleagues welcome the comments, as they provide avenues for further research. "Some of the authors of the letters were not yet comfortable with declaring these newly discovered glands . . . [and said] that they would like to see additional evidence, and also made very valid suggestions," Vogel tells *The Scientist.* "This actually really helps us to explore further and to build more evidence. Of course, then it's a matter of opinion, how much evidence you need to name something as a gland."

http://bit.ly/3qv6SpB

Every 8 Years, Swarms of Millipedes Stop Trains in Japan. Scientists Finally Know Why

Every eight years during fall, a plague of millipedes swarm train lines in mountainous Japan, earning them the nickname 'train millipedes'.

Jacinta Bowler

Working together, these small beasties (around 3 cm or 1.18 inches long) - which play a large role cycling nitrogen in Japan's larch forests - have forced trains to come to a skidding halt.

Up until now, scientists weren't quite sure what was causing them to swarm with such peculiar regularity, but a 50-year research project has finally confirmed that the species - *Parafontaria laminata armigera* (*P. l. a.*) - exists on a rare eight-year life cycle.

This confirmation is incredibly exciting, as cicadas are the only other known periodical animals with lifespans this long.

"This millipede needs seven years from egg to adult and one more year for maturation," the team writes in their new paper. "Thus, the eight-year periodicity of *P. l. a.* was confirmed by tracing the complete life history from eggs to adults in two different locations."

We don't know why cicadas emerge in 13- and 17-year intervals, but thanks to some incredible research, we do now understand the eight-year life cycle of the train millipedes.

Lead author and government ecologist Keiko Niijima first started conducting observations into these millipedes in 1972, and two

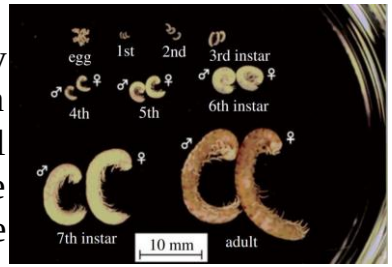
main sites were surveyed between one and five times per year for many of the years between then and 2016. It was quite an operation, and when they got to the two sites at Mt. Yatsu and Yanagisawa, the job wasn't exactly easy and quick either.

The train millipedes swarming. **(Keiko Niijima)**

"The soil to a depth of 0–5 cm was dug out, spread on a polyethylene sheet and the millipedes on the sheet were collected using forceps or an aspirator," the researchers explain.

"Then, the same procedure was repeated for 5–10, 10–15 and 15–20 cm depths."

Collecting any millipedes they found, they discovered that the millipedes have seven stages (called instars) of growing up, all of which stay in the soil and hibernate during winter and then molt in the summer.



(K. Niijima)

"The train millipedes undertake a molting in the summer every year and have seven larval instars," the researchers write. "They become adults by the eighth molting after eight years from egg deposition."

Then, the adults swarm on the surface in September and October, sometimes travelling up to 50 metres to get frisky before hibernating during the winter, and copulate again in late spring.

By August, the females have laid 400 to 1,000 eggs and the adults have all died – ready for another eight-year generation. As with cicadas, the millipede's eight years aren't all in sync everywhere.

In fact, the team suspects there are seven broods across the mountainous region of Central Japan that completed their lifecycle each in different years. That being said though, they don't move much, so a particular train line will continue to have the same issue every eight to 16 years from one brood.

Looking at historical records dating all the way back to the 1910s, the researchers were able to attribute nearly every reported millipede swarming to one of the seven broods.

"We have shown the existence of a periodical millipede, a new addition to periodical organisms with long life cycles: periodical cicadas, bamboos and some plants in the genus *Strobilanthes*," the team writes. "*Parafontaria laminata armigera* is the first record of periodical non-insect arthropod."

With arthropods and insects making up a huge percentage of all animals on Earth, and only a fifth having been identified or named, there's likely to be plenty more long periodic life cycles out there. All we've got to do is find them.

The research has been published in *Royal Society Open Science*.

http://bit.ly/39Jzntf

Warty pig is oldest animal cave art on record

The piggies were painted in Indonesian caves.

By Laura Geggel - Associate Editor

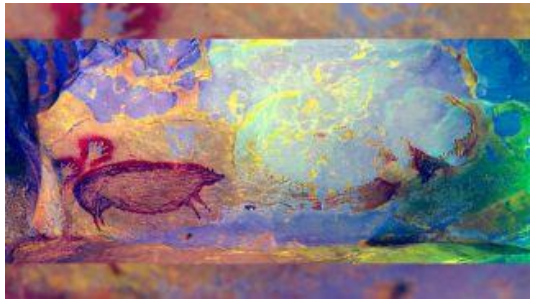
The oldest-known animal drawing in the world is a 45,500-year-old depiction of a hairy, warty pig on a cave wall in Indonesia, a new study finds.

The mulberry colored painting, drawn with the red mineral ochre, shows the profile of what is likely a Sulawesi warty pig (*Sus celebensis*), a wild stubby-legged beast with facial warts that can weigh up to nearly 190 pounds (85 kilograms). These pigs "are still found there today, although in ever-dwindling numbers," said study co-lead researcher Adam Brumm, a professor of archaeology at Griffith University's Australian Research Centre for Human Evolution.

The finding provides more evidence that ancient Indonesia was a hot spot for rock art, and that "the first rock art traditions probably did not arise in ice age Europe as long supposed," Brumm told Live

Science in an email.

In December 2017, Brumm and his colleagues found at least three warty pig drawings in Leang Tedongnge Cave, on Sulawesi, an Indonesian island that's slightly larger than Florida. This cave was in a small valley now inhabited by Bugis farmers, an enthic group in Indonesia. "There are no roads to this valley; getting there from the adjacent lowlands requires an arduous trek along a forest path that leads up into the limestone hills and ends at a narrow cave passage — this is the only entrance to the valley," Brumm said.



A digitally enhanced panorama of the warty pigs at Leang Tedongnge Cave, in Sulawesi, Indonesia. **(Image: © AA Oktaviana)**

So, despite the valley's proximity to the large city of Makassar, "according to the people who live in this valley, no Westerners had ever set foot in the place before," said Brumm, who worked with an international team from Australia and Indonesia on the study, published online Wednesday (Jan. 13) in the journal Science Advances.

Pigging out

Of the few pig drawings in the limestone cave, the most well-preserved one is the oldest. It shows a large pig — measuring about 4.5 by 1.8 feet (136 by 54 centimeters), with the outlines of two human hands painted above its rump. The hairy, tiny-tailed porker faces two or three other pigs, which are less well-preserved and appear to be having some kind of social interaction with the giant pig.

In a nearby cave, called Leang Balangajia 1, the team spotted an even larger painted pig on the ceiling, measuring about 6.1 by 3.6 feet (187 by 110 cm), with four stenciled hands on it. That cave chamber has at least two other animal paintings, but they are too damaged to decipher, the researchers said. A few anatomical clues hint that the rock art in both caves depicts adult male pigs — for instance, they're painted with impressive facial warts, which are larger in adult males than in females.

So, why were pigs popular subjects for the caves' artists?

Sulawesi warty pigs are unique to that island — they evolved there in isolation hundreds of thousands of years ago, Brumm said. Archaeological evidence suggests that humans hunted and even domesticated these pigs. "So, it seems clear that early humans interacted closely with this pig on various levels for a very long period of time," Brumm said. "In fact, the ice age artists of Sulawesi almost seem to have been obsessed with warty pigs, which is perhaps not surprising given their economic importance."

Dating queries

Previously, the oldest-known rock art depicting an animal, a Sulawesi warty pig found in another cave on the island, dated to at least 43,900 years ago, according to a 2019 study published in the journal Nature, which was also discovered by Brumm and colleagues, including Maxime Aubert, an archaeologist and geochemist at Griffith University. Meanwhile, the oldest known drawing (of any kind) made by a human is a 73,000-year-old hashtag painted on a rock flake from South Africa, Live Science previously reported.

To date the newfound rock art, the team sampled a few calcite minerals that had "grown" over the pigs after they were painted. The researchers did this by using uranium-series dating, a method that measures uranium's radioactive decay. When rainwater seeps through a limestone cave, it dissolves tiny amounts of uranium, which decays over time into the element thorium. By measuring the ratio of uranium to thorium in each mineral sample, the scientists determined when the minerals started growing over the paintings.

This technique revealed that the warty pig from Leang Tedongnge was at least 45,500 years old, while the swine on the ceiling from Leang Balangajia 1 dated back at least 32,000 years. In addition to being the oldest-known rock art painting of an animal, the Leang Tedongnge pig is the "earliest known representational work of art in the world," and possibly the earliest evidence of modern humans on Sulawesi, if one assumes that modern humans (and not a closely related human relative, like the Denisovans) painted the pigs, the researchers wrote in the study.

However, the researchers had a number of technical difficulties with the uranium–thorium dating, which they acknowledge, but which make the dates rough estimates, said David Pearce, an associate professor at the Rock Art Research Institute at the University of the Witwatersrand in South Africa, who was not involved with the research. "It is important to remember that they are relative ages ... rather than direct dates on the paintings themselves," Pearce told Live Science in an email.

The dating issues were also noted by João Zilhão, a professor at the Catalan Institution for Research and Advanced Studies (ICREA) at the University of Barcelona, who was not involved in the study. But "what this paper does is corroborate their previous finding that rock paintings were being made in Indonesia more than 43,900 years ago," he told Live Science.

http://bit.ly/3qmJN8C

Elsevier flips 160 journals to open access

Commercial publishing giant Elsevier is converting 160 subscription-based journals to fully open access models.

By Jamie Durrani

The move comes as the European open access initiative Plan S enters a crucial new stage.

The Coalition S movement behind Plan S noted that it has registered 160 Elsevier publications as 'transformative journals' – committing them to turning fully open access. Transformative journals must increase the proportion of their research articles that are immediately free to read by at least 5% per year. They must also commit to remove subscription fees as soon as 75% of their papers are published open access.

Coaltion S – a group comprising more than 20 major research funders – has stipulated that researchers receiving their support must publish their work in repositories or open access journals that are immediately free to read. While the initiative was first announced in 2018, the terms were fully implemented from 1 January this year. Elsevier states that of its 2600 journals, more than 500 are already open access.

http://bit.ly/2NcA7PU

Retinal cell transplant clears experimental hurdle toward treating blindness

Cells derived from adult human eye stem cells survived when transplanted into the eyes of monkeys

Retinal cells derived from adult human eye stem cells survived when transplanted into the eyes of monkeys, an important early step in the validation of this approach for treating blindness, according to a study by Liu, et al recently published in *Stem Cell Reports*. The retinal pigment epithelium (RPE), a layer of pigmented cells in the retina, is essential for sustaining normal vision. Blindness due to RPE dysfunction, such as macular degeneration, affects about 200 million people worldwide.

To restore this population of cells, researchers extracted retinal stem cells from donated cadaver adult eyes, grew them into RPE cells and transplanted them into the eyes of monkeys. These unique cells have the potential to serve as an unlimited resource of human RPE, with the possibility of donor compatibility matching.

The study is the first time the safety and feasibility of adult retinal stem cell-derived RPE transplants in non-human primates was

assessed. Researchers found that RPE patches transplanted into the monkey's eye stably integrated for at least three months with no serious side effects. What is more, the stem cell-derived RPE partially took over the function of the monkey RPE and was able to support normal photoreceptor function. Importantly, these cells did not cause retinal scarring.

Altogether, this demonstrates the feasibility of using adult retinal stem cell-derived RPE transplants to replace defective RPE as a possible treatment for macular degeneration. However, further experiments need to be conducted. This includes evidence to demonstrate adult retinal stem cell-derived RPE can restore vision in diseased non-human primate models, and eventually in regulatory human clinical trials. Nonetheless, this proof-of-principle study is an important early step in validating this approach, which is part of as international collaboration between the Icahn School of Medicine at Mount Sinai (New York), Institute of Molecular Cell Biology (A*STAR), Singapore Eye Research, National University of Singapore, and Eye Clinic Sulzbach (Germany).

http://bit.ly/3nYSYe4

Juno Maps Water Ice Across Northern Ganymede

Infrared observations from instruments on the Juno spacecraft cover regions of Ganymede not visible to Earth-based telescopes.

By Morgan Rehnberg

Jupiter's moon Ganymede is the largest planetary satellite in the solar system. It's also one of the most intriguing: Ganymede is the only moon with its own magnetic field, it is the most differentiated of all moons, and it likely possesses a subsurface ocean of liquid water. It was studied by the early Jupiter flybys made by the Pioneer and Voyager spacecraft, but our understanding today rests largely on observations made by NASA's Galileo orbiter from 1995 to 2003.

Mura et al. now report some of the first in situ observations of Ganymede since the end of the Galileo mission. They used the Jovian Infrared Auroral Mapper (JIRAM) on board NASA's Juno spacecraft to take images and spectra of the moon's north polar region. On 26 December 2019, Juno passed Ganymede at a distance of about 100,000 kilometers, enabling JIRAM to map this region at a spatial resolution of up to 23 kilometers per pixel.

As Juno flies past Ganymede, the spacecraft can observe physical locations on the moon's surface from a variety of angles. By comparing the brightness of these regions across a range of observation and illumination geometries, the authors developed a photometric model for Ganymede's surface reflectance. They observed that wavelength-dependent reflectance relationships sometimes break down in the vicinity of relatively fresh craters, perhaps because of a larger average size of ice grains in these regions.

Combining their model with spectral observations of the 2-micrometer water ice absorption band allowed the authors to map the distribution of water ice in the north polar region. Where these estimates overlapped with maps derived from Earth-based telescopic observations, the researchers found largely good agreement. This congruence enabled them to extend the global water ice map for Ganymede to much more northerly latitudes.

Observations in other spectral bands also revealed the presence of nonwater chemical species on the surface of Ganymede, including possible detections of hydrated magnesium salts, ammonia, carbon dioxide, and a range of organic molecules. The authors note that 2020 offered additional opportunities for Juno to make polar observations of Ganymede, as does 2021, and suggest that continuing observations from JIRAM will help set observation strategies in future observing campaigns like the Europa Clipper and Jupiter Icy Moons Explorer (JUICE) missions.

(*Journal of Geophysical Research: Planets*, https://doi.org/10.1029/2020JE006508, 2020)
Citation: *Rehnberg, M. (2021), Juno maps water ice across northern Ganymede, Eos, 102, https://doi.org/10.1029/2021EO153447. Published on 14 January 2021.*

http://wb.md/2Y1h5yd

'The Most Horrific Time of My Career': When Years of Published Work Are Built on an Error

In September 2019 Nicola Smith, a molecular pharmacologist in Australia, faced a brutal decision.

Retraction Watch Staff

She'd realized that she'd made a mistake — or rather, failed to catch a mistake in her group's research before the crippling error was published — in two academic articles which were the culmination of years of work. And she could either tell the world, or pretend it never happened.

Her students had been having trouble reproducing lab data. Once she looked into it and she figured out why, she told them, "Guys, you're not going to believe this." A cloning error had ensured the experiments were doomed to fail from the start.

If she came clean, she knew that at least one of the articles would most likely be retracted and she'd have to live with a lasting mark on her and her team's record. "What can I do to minimize the impact" on her two students? Smith thought at the time.

In particular, Tony Ngo,who was first author on both papers and had recently finished a PhD in her lab, was looking forward to a future in academia. Smith was terrified of tarnishing his prospects.

What was to stop her from just keeping quiet about it?

Smith, then at the Victor Chang Cardiac Research Institute in Sydney, studied G protein-coupled receptors – which are the largest class of receptors, are often targeted by drugs, and allow many hormones to interact with cells in the body.

She specialized in "orphan" G protein-coupled receptors, those activated by unknown molecular partners. At that time, she was looking into one labeled GPR37L1, which exists in humans and affects the cerebral development of mice. The research community studying the receptor is small and scientists are still trying to decipher its activity. "There is a lot of mystery around this receptor," says Irina Kufareva of the University of California, San Diego, who collaborated with Smith and was co-senior author on one of the studies.

In Smith's area of study, researchers can't observe a receptor directly. Instead, they use a genetic vector to carry it inside cells, then pay close attention to the resulting activity – looking for telltale chemical indicators of what the receptor might be doing.

In 2016, her group published a paper in *Science Signaling* in which they reported what happened when they cut off the head of the protein in question: the receptor's activity dropped – effectively switching activity on and off. They were able to show that the G protein-coupled receptor could be active without being triggered and could be controlled by severing that first chunk.

An indicator which helped them monitor this activity had also been present in their previous tests using yeast cells. Which was encouraging — now with human cells they were seeing similar results.

Then in 2019 an honors student (a post-undergraduate researcher) in Smith's lab was trying to make genetic constructs with mutated receptors to compare how they behave in cells with the natural ones. The constructs required for the experiments were comprised of a vector embedded with the genes of interest.

When he couldn't, they figured the failure was simply because the process was "fiddly," as James Coleman, then a post-doc in Smith's lab and co-first author on the paper with Ngo, puts it. The trouble persisted until August 2019, when they gave up and decided to order ready-made versions of the constructs instead.

But when the constructs arrived, and the lab tried to recreate the

past experiments, the new construct "was behaving completely unlike the one that we had been working with previously – the one that we had published with," Coleman says.

In September they sequenced the troublesome genes and found they had been using the wrong vector to carry them.

That wasn't all. Not only was the gene put in the wrong vector, the receptor gene itself — a string of genetic information — was inserted into the vector backwards so it couldn't be read correctly. Even one of those catastrophic errors would have almost certainly invalidated her findings, but both together killed all chances of a meaningful result.

The reason it was so hard to catch the snafu sooner was that normally when one makes a mistake like this, Smith says, the experiment simply wouldn't work. Remarkably, not only had the experiment worked, it had produced results that were in line with what the researchers had seen in related experiments. Now that the team had arrived at the root of the problem, their hearts sank as it became clear that their once-promising results were a fluke.

After realizing her group's mistake, Smith turned to a trusted colleague for advice. She says the colleague told her that "despite the fact that you really care about this receptor, no one else in the world really gives a toss about it."

In essence, the sentiment was: Weigh the damage done by letting an error affect a few niche publications against the potential fallout and long-term career damage it would do to her and her team. And for that day Smith was almost convinced that keeping quiet to protect her team was the best option.

After hours of turmoil, Smith realized that her colleague's line of reasoning – that she could ignore her error and just move on – was "utter bullshit," she says. It didn't matter whether or not anyone else cared about the receptor; feigning ignorance was wrong.

You just have to do the right thing, Smith says, "even though it's the most painful thing you'll ever do." She couldn't spend the rest of her career wondering how much damage her error would cause. She alerted her institutes about the error (both Victor Chang and the University of New South Wales, with which it's affiliated) and, shortly after, the journals involved. She decided that total transparency was the best path.

After making that choice, "The weight just lifted off my shoulders; it was the right decision," Smith says. She was committed to doing the right thing, but knew she'd have to face consequences.

Months after Smith's realization of the error, she found herself in the heart of a storm. She was immensely stressed, getting regular phone calls from the investigators at her institute, whose funding body required them to launch a preliminary investigation to see if there were signs of misconduct, Smith says.

She was organizing experiments for her students to contextualize the error. One of those students was Brendan Wilkins, a research assistant who often worked until midnight.

Smith did all of this while taking care of her two boys, one age three, the other not yet one. The ordeal had pulled her away from her family and began not long after she returned from maternity leave. "[M]y three-year-old started mimicking me at the computer, saying: 'Sorry, Mummy, I'm doing work,'" because it was so all consuming, Smith says.

But at the worst of it, she got an email from another researcher which strengthened her resolve. The researcher had a question about the *Science Signaling* paper, which she and her co-authors had asked the journal to retract. It would be, but at the time the forward facing text was unchanged. That moment drove home to her the importance of correcting the record. Scientists spend so much time and energy struggling to reproduce genuine data, Smith says, there isn't room in the literature for known errors.

Smith explained what had happened and asked the researcher to be

discreet while the retraction was being worked out.

Retraction Watch © 2021

http://bit.ly/38RC0tx

Designer cytokine makes paralyzed mice walk again

The researchers published their report in the Journal Nature Communications from 15 January 2021.

When the communication breaks down

Spinal cord injuries caused by sports or traffic accidents often result in permanent disabilities such as paraplegia.

This is caused by damage to nerve fibers, so-called axons, which carry information from the brain to the muscles and back from the skin and muscles. If these fibers are damaged due to injury or illness, this communication is interrupted.

Since severed axons in the spinal cord can't grow back, the patients suffer from paralysis and numbness for life.

To date, there are still no treatment options that could restore the lost functions in affected patients.

Designer protein stimulates regeneration

In their search for potential therapeutic approaches, the Bochum team has been working with the protein hyper-interleukin-6.

"This is a so-called designer cytokine, which means it doesn't occur like this in nature and has to be produced using genetic engineering," explains Dietmar Fischer.

His research group already demonstrated in a previous study that hIL-6 can efficiently stimulate the regeneration of nerve cells in the visual system.

In their current study, the Bochum team induced nerve cells of the motor-sensory cortex to produce hyper-Interleukin-6 themselves.

For this purpose, they used viruses suitable for gene therapy, which they injected into an easily accessible brain area.

There, the viruses deliver the blueprint for the production of the protein to specific nerve cells, so-called motoneurons.

Since these cells are also linked via axonal side branches to other nerve cells in other brain areas that are important for movement processes such as walking, the hyper-interleukin-6 was also transported directly to these otherwise difficult to access essential nerve cells and released there in a controlled manner.

Applied in one area, effective in several areas

"Thus, gene therapy treatment of only a few nerve cells stimulated the axonal regeneration of various nerve cells in the brain and several motor tracts in the spinal cord simultaneously," points out Dietmar Fischer.

"Ultimately, this enabled the previously paralyzed animals that received this treatment to start walking after two to three weeks.

This came as a great surprise to us at the beginning, as it had never been shown to be possible before after full paraplegia."

The research team is now investigating to what extent this or similar approaches can be combined with other measures to optimize the administration of hyper-Interleukin-6 further and achieve additional functional improvements.

They are also exploring whether hyper-interleukin-6 still has positive effects in mice, even if the injury occurred several weeks previously.

"This aspect would be particularly relevant for application in humans," stresses Fischer. "We are now breaking new scientific ground.

These further experiments will show, among other things, whether it will be possible to transfer these new approaches to humans in the future."

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Original publication

Marco Leibinger, Charlotte Zeitler, Philipp Gobrecht, Anastasia Andreadaki, Günter Gisselmann, Dietmar Fischer: Transneuronal delivery of hyper-IL-6 enables functional recovery after severe spinal cord injury in mice, in: Nature Communications, 2021, DOI: 10.1038/s41467-020-20112-4, https://rdcu.be/cdCob

http://bit.ly/3qtFmch

Skin Sheltered from Sunlight Still Gathers UV-Linked Mutations

Whole-genome sequencing reveals a wide range of UV-induced DNA changes in human skin cells, and lighter skin collects more mutations, sometimes to "sky high" levels.

Abby Olena

A genomic study of skin cells shows that there's a wide range in the normal number of somatic mutations that arise from exposure to UV light and that these mutations are independent of age. The work, which was published today (January 14) in *PLOS Genetics*, also confirms that darker skin is more protected from UV-related mutations—something that scientists have long suspected.

Researchers "have this idea that the pigment protects you from the DNA damage that sunlight causes, and that's something they really nicely show," says Ruben van Boxtel, a cancer biologist at the Princess Máxima Center for Pediatric Oncology in the Netherlands who did not participate in the work. Previous sequencing efforts have mostly been done in Caucasians, he adds, but these authors include samples from people with darker skin.

When Natalie Saini joined Dmitry Gordenin's lab at the National Institute of Environmental Health Sciences (NIEHS) in North Carolina in 2014, tons of cancer genomes had been sequenced from groups worldwide. It wasn't yet clear, though, the significance of many of the mutations researchers were seeing. "In order to say that cancer genomes have more mutations or less mutations or even anything [different] from normal, you had to know what normal was," says Saini, who now runs her own lab at the Medical University of South Carolina.

Gordenin, Saini, and colleagues started by sequencing fibroblasts from skin biopsies taken from the hip and forearm of two individuals. In a 2016 study, they reported a range of somatic mutations and could see a UV-related mutation signature in forearms that was much greater than in hips, indicating that sun exposure made a difference in mutation rate.

"Then the question was—that was just two people, and they were both Caucasian and male—so what does the rest of the world look like?" Saini tells *The Scientist*. For the current study, the researchers isolated 34 fibroblasts and five melanocytes from biopsies taken from the healthy, noncancerous skin of the hips of 21 volunteers, ranging in age from 25 to 79 years, and expanded clones of those cells in culture. According to Saini, getting skin biopsies from people without cancer was key to the group's goal of understanding mutation rates in normal tissue. Previous studies have used cells isolated from people who come in for cancer therapy, Saini explains. "When they're taking biopsies from the tumors, they also try and take normal tissue, but this is not a healthy individual."

The researchers isolated and sequenced genomic DNA from each of these cell lineages. Because they knew that UV light is more likely to cause mutations at specific sequence patterns in the genome, the team looked for those mutational signatures and evaluated how much they were enriched compared to all other mutations. They determined that UV-induced mutations were prevalent in all the cells they looked at, ranging from 400 to more than 14,000 base substitutions. The incidence of UV-related mutations did not increase with the age of the donors nor was it related to sex.

Skin cells from Black individuals carried a much lower median mutational load—about 700 base substitutions—than the median of 1,800 base substitutions seen in cells from white donors. Mutations unrelated to UV light damage did not differ between the cells of the two groups, pointing to the protective role that the melanin in skin provides against sun exposure.

"If you look at the numbers of mutations that they detect, they're

using quite stringent strategies, so . . . the numbers here are probably on the lower end of what [the cells] actually have," says Maria Eriksson, who studies genetic mechanisms of aging at the Karolinska Institute in Sweden and was not involved in the work. The "open question is, does it matter if you have all these mutations?"

Along these lines, another important question is, "when is a normal cell not a normal cell anymore?" van Boxtel tells *The Scientist.* "Normal cells are actually not as normal as we think they are," he adds. "Some of these mutations are really sky high. Is there a limit to the number of mutations a normal cell can have or do you eventually become something else?"

"For skin, I think we gave a pretty good baseline" of what is normal in terms of somatic mutation rates, says Gordenin. "Baseline levels of genome changes in skin defined by our study may help researchers to develop testing procedures for detecting high, disease-prone levels in otherwise healthy individuals."

N. Saini et al., "UV-exposure, endogenous DNA damage, and DNA replication errors shape the spectra of genome changes in human skin," PLOS Genet, doi:10.1371/journal.pgen.1009302, 2021.

http://bbc.in/3p5qqr2

Covid: 'Convalescent plasma no benefit to hospital patients'

A potential treatment for Covid using blood plasma does not reduce deaths among hospital patients, trials show.

By Philippa Roxby Health reporter

The results are a blow to researchers and the NHS, which led the drive to collect plasma donations. This arm of the Recovery trial, which is investigating a number of promising Covid treatments, has now been closed. The Oxford researchers involved say they are "incredibly grateful" for the contribution of patients across the country.

Donations of plasma have been temporarily suspended, according to NHS Blood and Transplant. There had been huge international interest in the role of convalescent plasma as a possible treatment for hospital patients with Covid-19.

The treatment involves blood plasma being taken from people who have recovered from the disease - which contains antibodies to coronavirus - and transfused into seriously ill patients.

It was hoped the plasma donation would give the recipient's struggling immune system a boost to fight off Covid.

The NHS had been urging people to donate, particularly men who are thought to have higher levels of antibodies in their blood.

'Value of trials'

But early analysis of 1,873 deaths in a study of 10,400 UK patients shows the treatment made "no significant difference".

In the group treated with convalescent plasma, 18% of patients died within 28 days - the same figure for the group given standard treatment. Patients in the study are still being followed up and the final results will be published shortly.

Earlier this week, a separate study showed no evidence that the same treatment improved outcomes for patients in intensive care.

Martin Landray, chief investigator and professor of medicine and epidemiology at the Nuffield Department of Population Health, University of Oxford, said the Recovery trial showed "the value of large randomised trials to properly assess the role of potential treatments". The trial is still investigating other treatments, including tocilizumab, aspirin and an antibody cocktail.

Prof Peter Horby, who also worked on the trial, said the largest ever trial of convalescent plasma "was only possible thanks to the generous donation of plasma by recovered patients and the willingness of current patients to contribute to advancing medical care".

"While the overall result is negative, we need to await the full

results before we can understand whether convalescent plasma has any role in particular patient sub-groups," he said.

http://bit.ly/2XNxLc7

Japanese scientists discover medical agent that could slow aging-related diseases

The discovery is expected to help improve the treatment and prevention of age-associated diseases.

A Japanese research team has discovered a medical agent capable of only removing senescent cells, which can cause aging-related diseases such as arteriosclerosis and diabetes.

The team, including researchers from the University of Tokyo, Niigata University and Kyushu University, succeeded in improving symptoms of such diseases in mice through the use of the medical agent.

The discovery is expected to help improve the treatment and prevention of such age-associated diseases. A paper about the finding was published in the U.S. journal Science on Friday.

When cells come under stress they transform into senescent cells and accumulate in the body with aging.

Previous research with elderly mice has shown that it is possible to delay the development of arteriosclerosis and kidney disorder by removing senescent cells from the body using a special method.

But the use of a medical agent in the removal of such cells had not been discovered until now.

Makoto Nakanishi, a professor at the University of Tokyo's Institute of Medical Science, and other team members looked for the gene necessary for a senescent cell to survive and identified glutaminase 1, or GLS1, a gene related to glutamine metabolism.

The team also found that the inside of a senescent cell is acidified due to an abnormality in cell organelles, and GLS1 actively works to neutralize inside of the cell and keep it alive.

When administered with an inhibitor of GLS1, senescent cells in a variety of organs in elderly mice were eliminated and improvements in kidney, lung and liver functions were confirmed.

Improvements were also seen in mice with arteriosclerosis or diabetes. The inhibitor is expected to have similar effects on the human body, as it has been learned that GLS1 in the human body also becomes more active with aging.

The inhibitor of GLS1 has already been used in clinical trials as a candidate for cancer treatment. "It may also be effective for treating other age-associated diseases such as dementia," Nakanishi said. "It would be great if we could try to carry out clinical trials (for such use) in the next five to 10 years."

http://bit.ly/3oSRpzf

Why Some of Darwin's Finches Evolved to Become Vampire Finches

There are indeed "vampire finches" that feast on the blood of much larger birds

Kiyoko Gotanda, Et Al., The Conversation

For most people, the word "vampire" brings to mind Dracula or perhaps slayers such as Blade or Buffy; or maybe even the vampire bats of South America. Few will think of a small and rather lovely bird – the finch.

(Jaime Chaves)

But there are indeed "vampire finches" that feast on the blood of much larger birds, and they were introduced to the world in a fantastic segment of *Perfect Planet*, the new series narrated by David Attenborough for the BBC. For us, these finches needed no introduction as we have studied them closely.

These birds are found on the Galápagos Islands, a volcanic archipelago located about 1,000 kilometres (600 miles) off the coast of Ecuador. The islands are a biodiversity hotspot in part because of

their isolation. Organisms that somehow make it to the Galápagos must adapt to the harsh conditions or go extinct.

One such group of organisms is the Darwin's finches. Named after the naturalist Charles Darwin, who collected examples on his famous voyage aboard the HMS Beagle, this group of finches consists of several species that have evolved from a common ancestor.

Each species has evolved a different bill size and shape which allows it to exploit different food items. For example, the cactus finch has a long thin bill that allows it to consume the nectar from of cactus flowers. Some species have bills that are better at crushing seeds, while others are better at consuming insects or plants.

It makes sense that different species of finches evolved to feed on different types of food items on the Galápagos, but where did blood-feeding come from?

How blood-sucking evolved

The vampire finches are found only on Wolf and Darwin, the two northernmost islands of the archipelago and remote even by Galápagos standards. Both islands are tiny, each less than a square mile, and are separated from the larger islands by 100 miles of open ocean. Freshwater is extremely rare and some food can disappear entirely during the dry season.

At some point in the last half-million years – recent in evolutionary terms – finches arrived on Wolf and Darwin and began to co-exist with large seabirds which nest on the islands, such as red-footed and Nazca boobies.

Over time, it seems the finches likely evolved to eat parasites found in the feathers and on the skin of the boobies. This was "mutualism" in action: the boobies benefited from parasite removal, and the finches benefited by having an alternative to their usual diet of nectar, seeds, and insects which can disappear during the dry season.

Eventually, however, the removal of parasites led to open skin lesions on the boobies, allowing the finches to consume blood.

The finches even learned to pierce skin at the base of young feathers to access the blood directly, no longer needing the insect parasites anymore. Thus, the finches capitalised on an alternative food resource, blood from the boobies, and earned themselves the nickname "vampire finches".

It's hard to know exactly how much of the finch's diet is booby blood, but our unpublished data suggests it's about a tenth.

Natural selection appears to have fine-tuned the vampire finch beak for skin-piercing and blood-sucking, as the birds have evolved particularly long and pointy beaks compared to non-blood-feeding populations on other islands. And once a blood-feeder pierces the skin, it still needs a way to consume and digest the blood.

When we studied the microbes found in the guts of these vampire finches in search of adaptations we found a very different microbiome from any other species of Darwin's finches, presumably caused by the blood diet.

What it's like to see in person

Two of us, Daniel and Jaime, visited Darwin and Wolf to study these fascinating finches on islands that are very rarely visited, even by researchers.

Getting there was extremely challenging as there are no beaches for landing a boat. We had to approach the cliffs in a small dinghy and then wait for a brief gap in the waves before jumping onto sharp, black lava rocks.

But this isolation means the vampire finches are plentiful, and the dense breeding colonies of boobies made it easy to envision how this strange blood-sucking behaviour could have evolved.

The boobies are incredibly vulnerable when tending to nests and chicks, as they are reluctant to abandon them, even temporarily.

We observed scores of vampire finches clamouring all over the backs, tails, and wings of boobies, opening up substantial wounds

with their sharp beaks, and drinking their fill of blood.

Interestingly, the finches seem to act like a true parasite, inflicting enough damage to secure a meal without excessively harming the host.

For the boobies, the whole experience really is very similar to a human being attacked by mosquitos. Though they can tolerate the finches, the small bloodsuckers are a nuisance that the boobies do try to get rid of. And when it all gets too much, they can be forced to fly away.

And who can blame them? When we captured finches to collect samples, and found gullets full of blood, and beaks stained red. It was evident that the little vampires were not merely lapping up a few drops of blood.

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