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A new theory for how memories are stored in the brain

Revolutionary new theory for understanding brain and memory function

Research from the University of Kent has led to the development of the MeshCODE theory, a revolutionary new theory for understanding brain and memory function. This discovery may be the beginning of a new understanding of brain function and in treating brain diseases such as Alzheimer's.

In a paper published by *Frontiers in Molecular Neuroscience*, Dr Ben Goult from Kent's School of Biosciences describes how his new theory views the brain as an organic supercomputer running a complex binary code with neuronal cells working as a mechanical computer. He explains how a vast network of information-storing memory molecules operating as switches is built into each and every synapse of the brain, representing a complex binary code. This identifies a physical location for data storage in the brain and suggests memories are written in the shape of molecules in the synaptic scaffolds.

The theory is based on the discovery of protein molecules, known as talin, containing "switch-like" domains that change shape in response to pressures in mechanical force by the cell. These switches have two stable states, 0 and 1, and this pattern of binary information stored in each molecule is dependent on previous input, similar to the Save History function in a computer. The information stored in this binary format can be updated by small changes in force generated by the cell's cytoskeleton.

In the brain, electrochemical signalling between trillions of neurones occurs between synapses, each of which contains a scaffold of the talin molecules. Once assumed to be structural, this research suggests that the meshwork of talin proteins actually represent an array of binary switches with the potential to store information and encode memory.

This mechanical coding would run continuously in every neuron and extend into all cells, ultimately amounting to a machine code coordinating the entire organism. From birth, the life experiences and environmental conditions of an animal could be written into this code, creating a constantly updated, mathematical representation of its unique life.

Dr Goult, a reader in biochemistry, said: 'This research shows that in many ways the brain resembles the early mechanical computers of Charles Babbage and his Analytical Engine. Here, the cytoskeleton serves as the levers and gears that coordinate the computation in the cell in response to chemical and electrical signalling. Like those early computation models, this discovery may be the beginning of a new understanding of brain function and in treating brain diseases.'

"*The Mechanical Basis of Memory - The MeshCODE theory" is published in Frontiers in Molecular Neuroscience (Dr Ben Goult, School of Biosciences, University of Kent).*
https://www.frontiersin.org/articles/10.3389/fnmol.2021.592951/full

http://bit.ly/3kJXaOv

New magnesium alloy shows exceptional corrosion resistance

Exceptionally low corrosion rate approaches stainless magnesium

By Lucy Balshaw

Scientists in Germany have created an alloy with an exceptionally low corrosion rate – lower, even, than ultra high-purity magnesium – that they say approaches stainless magnesium, by alloying pure magnesium with tiny amounts of calcium.

Due to its low weight, high strength, abundance in the Earth’s crust and excellent electrochemical properties, magnesium is widely used in automotive, aerospace, electronic, biomedical and energy-storage applications. In particular, magnesium’s weight makes it attractive from a sustainable perspective – it is significantly lighter than

aluminium, so replacing aluminium with stainless magnesium in cars and aeroplanes could reduce fuel consumption and carbon dioxide emissions. However, using magnesium on an industrial scale is limited because it corrodes in aqueous environments.

The team tested their new alloy alongside two commercial alloys by immersing them in 3.5wt% NaCl solution for 6 months.

'Our magnesium–calcium alloys were prepared by conventional casting processes,' explains Min Deng from the Helmholtz Centre for Materials and Coastal Research in Geesthacht. 'Pure magnesium and pure calcium were melted at high temperatures in a steel crucible. Then, the melt was poured into a steel mould. After cooling to room temperature, the alloys were ready for use.'

By using only tiny amounts of calcium, the new alloy retains the properties of pure magnesium. However, it can resist corrosion because the calcium reduces the cathodic water reduction kinetics, allows the development of a protective surface film and stabilises impurities (such as iron and silicon) within the alloy.

Coating or alloying magnesium with elements such as lithium, aluminium or arsenic, is a common way to hold back corrosion. 'Compared to existing alloying [compositions], the addition of calcium broadens the practical applications of magnesium alloys an implant material, since calcium is harmless to the human body. Previous attempts to develop high corrosion-resistant magnesium alloys have always involved delicate and complicated processes,' explains Linqian Wang, another member of the Helmholtz team. 'In comparison, the processing route for [our] magnesium–calcium alloy with [its] superior performance is quite simple, eco-efficient and economical.'

The alloy could have 'biomedical applications, such as scaffolds and implants, because it seems to reduce significantly the formation of hydrogen bubbles, [which are] common in existing magnesium implant materials, [and] the formed corrosion products are not expected to be toxic,' comments Polina Volovitch, who studies corrosion at Chimie ParisTech in France. 'Application in aqueous batteries could also be [possible].'

'Practical applications of stainless magnesium are many and varied. Certainly portable electronics come to mind, but as a wonder material, the world is magnesium's oyster,' adds Nick Birbilis, who specialises in material sustainability and corrosion science at the Australian National University. 'Steel came before skyscrapers, so let's see what magnesium will bring us.'

References *M Deng et al, Mater. Horiz., 2021, **8**, 589 (DOI: 10.1039/d0mh01380c)*

http://bit.ly/3qqV35W

In a Momentous Discovery, Scientists Show Neanderthals Could Produce Human-Like Speech

Our Neanderthal cousins had the capacity to both hear and produce the speech sounds of modern humans, a new study has found.

Michelle Starr

Based on a detailed analysis and digital reconstruction of the structure of the bones in their skulls, the study settles one aspect of a decades-long debate over the linguistic capabilities of Neanderthals.

"This is one of the most important studies I have been involved in during my career," said palaeoanthropologist Rolf Quam of Binghamton University. "The results are solid and clearly show the Neanderthals had the capacity to perceive and produce human speech. This is one of the very few current, ongoing research lines relying on fossil evidence to study the evolution of language, a notoriously tricky subject in anthropology."

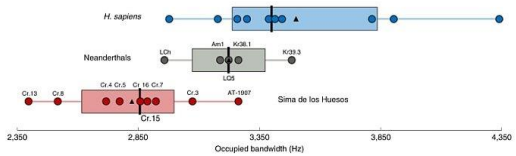
The notion that Neanderthals (*Homo neanderthalis*) were much more primitive than modern humans (*Homo sapiens*) is outdated, and in recent years a growing body of evidence demonstrates that they were much more intelligent than we once assumed. They

developed technology, crafted tools, created art and held funerals for their dead.

Whether they actually spoke with each other, however, has remained a mystery. Their complex behaviors seem to suggest that they would have had to be able to communicate, but some scientists have contended that only modern humans have ever had the mental capacity for complex linguistic processes.

Whether that's the case is going to be very difficult to prove one way or another, but the first step would be to determine if Neanderthals could produce and perceive sounds in the optimal range for speech-based communication.

So, using a bunch of really old bones, this is what a team led by palaeoanthropologist Mercedes Conde-Valverde of the University of Alcalá in Spain set out to do.



***The occupied bandwidth of modern humans (blue), Neanderthals (grey) and the Sima hominin (red).* (Conde-Valverde et al., Nat. Ecol. Evol., 2021)**

They took high-resolution CT scans of the skulls of five Neanderthals to create virtual 3D models of the ear structures. They also modeled the ear structures in *Homo sapiens*, and a much older fossil - the skull of a Sima de los Huesos hominin, also known as the Sima hominin, the ancestor of Neanderthals, dating back to around 430,000 years ago.

A model of the hearing capacity of these structures from the field of auditory bioengineering was then employed to understand frequency range to which the ears were most sensitive, also known as the occupied bandwidth. For modern humans, the occupied bandwidth is the human vocal range.

The team found that Neanderthals had better hearing in the 4 to 5 kilohertz range than the Sima ancestor, and that the Neanderthal occupied bandwidth was closer to that of modern humans than that of the Sima hominin. This optimization strongly suggests that Neanderthals needed to hear each other's voices.

"This really is the key," Conde-Valverde said. "The presence of similar hearing abilities, particularly the bandwidth, demonstrates that the Neanderthals possessed a communication system that was as complex and efficient as modern human speech."

Interestingly, the occupied bandwidth of Neanderthals extended into frequencies above 3 kilohertz that are primarily involved in consonant production. This, the team noted, would distinguish Neanderthal vocalizations from the vowel-based vocalizations of non-human primates and other mammals.

"Most previous studies of Neanderthal speech capacities focused on their ability to produce the main vowels in English spoken language," Quam said.

"However, we feel this emphasis is misplaced, since the use of consonants is a way to include more information in the vocal signal and it also separates human speech and language from the communication patterns in nearly all other primates. The fact that our study picked up on this is a really interesting aspect of the research and is a novel suggestion regarding the linguistic capacities in our fossil ancestors."

Having the anatomy capable of producing and hearing speech doesn't necessarily mean that Neanderthals had the cognitive ability to do so, the researchers cautioned. But, they point out, we have no evidence that the Sima hominins exhibited the complex symbolic behavior, such as funerals and art, that we've found associated with Neanderthals.

This difference in behavior parallels the difference in hearing capacity between Neanderthals and Sima hominins, which, the researchers say, suggests a coevolution of complex behaviors and the ability to communicate vocally.

"Our results," they wrote in their paper, "together with recent discoveries indicating symbolic behaviors in Neanderthals, reinforce the idea that they possessed a type of human language, one that was very different in its complexity and efficiency from any other oral communication system used by non-human organisms on the planet."

The research has been published in *Nature Ecology & Evolution*.

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People Are Accidentally Poisoning Themselves Trying to Treat COVID With a Horse Drug

People are trying to treat and prevent COVID-19 by taking ivermectin, a medication commonly used to de-worm horses – and they are poisoning themselves in the process.

Canela Lopez

ABC News reported an uptick in calls to poison control centers linked to the drug. The Missouri Poison Center alone has seen a 40 to 50 call increase in the regular amount of messages they would receive a day prior to the pandemic.

Experts are urging people to avoid the lure of fake "cures," which could cause health problems as bad or worse than a COVID-19 infection.

Rather than waiting to get the drug through proper channels, people are instead getting equestrian prescriptions through their vets and using horse-sized doses on themselves, Julie Weber, president of the American Association of Poison Control Centers, told ABC News.

"We just had a case of someone using a veterinary source of ivermectin, a horse medication, that contains a significantly larger dose of the drug," Weber told ABC News.

Why people are trying ivermectin

The buzz around ivermectin has been generated by the FLCCC, the Front Line COVID-19 Critical Care Alliance (FLCCC), which formed at the start of the pandemic. It comprises critical care workers who previously bonded over the controversial use of vitamin C for sepsis, MedPage Today reported.

US regulators say there is not enough robust evidence or safety data to recommend ivermectin as a cure, treatment, or preventative medicine for COVID-19.

While the FLCCC has held press conferences saying studies show the drug could fight against the novel coronavirus, public health agencies and many experts say the research is lacking.

The National Institutes of Health issued a statement earlier this month, refusing to support the use of ivermectin to treat COVID-19 until clinical trials in humans find it to be safe and effective. The US Food and Drug Administration has also told Americans not to self-administer ivermectin intended for animals.

"I want it to work, but at the same time, this whole thing feels like déjà vu of the first two months of the pandemic when we weren't decided about hydroxychloroquine," Dr. Zain Chagla, an infectious diseases physician at McMaster University, told MedPage Today. "We don't want to come around a year later saying it didn't help and it may have hurt."

Ivermectin can be tolerated in small doses but can poison an adult in large quantities

Ivermectin is commonly used as an anti-parasite cream on dogs, cats, and horses. It can eliminate lice, scabies, and worms in mammals. While smaller doses of the medication can be tolerated by humans, with few side effects aside from nausea, rashes, and increased heart rate, taking a dose of ivermectin intended for an animal the size of a compact car can poison you.

According to the Missouri Poison Center, serious overdoses of ivermectin can result in seizures, coma, lung issues, and heart problems.

The Missouri Poison Center recommends people refrain from

taking their pet's medication and instead wait to get one of the COVID-19 vaccines or seek medical attention if they believe they have been infected with the coronavirus.

According to the Centers for Disease Control and Prevention, the number of people who have accidentally poisoned themselves with household cleaners trying to disinfect their homes has jumped by 20 percent since the beginning pandemic.

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Secrets of sealed 17th century letters revealed by dental X-ray scanners

In a world first, an international team of researchers has read an unopened letter from Renaissance Europe—without breaking its seal or damaging it in any way.

by Queen Mary, University of London

The research, published in *Nature Communications*, describes how an X-ray scanner used in dental research and 'virtual unfolding' allowed the interdisciplinary team to read the contents of a securely and intricately folded letter which has remained unopened for 300 years, while preserving its valuable physical evidence.

A highly sensitive X-ray microtomography scanner, developed at Queen Mary University of London's dental research labs, was used to scan a batch of unopened letters from a 17th-century postal trunk full of undelivered mail.

Letterpacket DB-1627 was virtually unfolded and read for the first time since it was written 300 years ago. The letter contains a message from Jacques Sennacques dated 31 July 1697, to his cousin Pierre Le Pers, a French merchant, for a certified copy of a death notice of one Daniel Le Pers. Also visible is a watermark in the center of the paper containing an image of a bird. **Credit: Unlocking History Research Group archive.**

The senders of these letters had closed them using 'letterlocking' - the historical process of intricately folding and securing a flat sheet of paper to become its own envelope. Letterlocking was common practice for secure communication before modern envelopes came into use, and is considered to be the missing link between ancient physical communications security techniques and modern digital cryptography.

Until now these letterpackets could only be studied and read by cutting them open, often damaging the historical documents. Now the team have been able to examine the letters' contents without irrevocably damaging the systems that secured them.

Professor Graham Davis from Queen Mary University of London said: "We designed our X-ray scanner to have unprecedented sensitivity for mapping the mineral content of teeth, which is invaluable in dental research. But this high sensitivity has also made it possible to resolve certain types of ink in paper and parchment. It's incredible to think that a scanner designed to look at teeth has taken us this far."

Dr. David Mills from Queen Mary University of London said: "We've been able to use our scanners to X-ray history. The scanning technology is similar to medical CT scanners, but using much more intense X-rays which allow us to see the minute traces of metal in the ink used to write these letters. The rest of the team were then able to take our scan images and turn them into letters they could open virtually and read for the first time in over 300 years."

This process revealed the contents of a letter dated July 31, 1697. It contains a request from Jacques Sennacques to his cousin Pierre Le Pers, a French merchant in The Hague, for a certified copy of a death notice of one Daniel Le Pers (full transcript and images available). The letter gives a fascinating insight into the lives and concerns of ordinary people in a tumultuous period of European history, when correspondence networks held families, communities,

and commerce together over vast distances.

Following the X-ray microtomography scanning of the letter packets, the international team then applied computational algorithms to the scan images to identify and separate the different layers of the folded letter and 'virtually unfold' it.

A seventeenth-century trunk of letters bequeathed to the Dutch postal museum in The Hague. The trunk belonged to one of the most active postmaster and postmistress of the day, Simon and Marie de Brienne, a couple at the heart of European communication networks. The chest contains an extraordinary archive: 2600 "locked" letters sent from all over Europe to this axis of communication, none of which was never delivered. Sealed letterpackets from this trunk were scanned by X-ray microtomography and "virtually unfolded" to reveal their contents for the first time in centuries. **Credit: Unlocking History Research Group archive.**

The authors suggest that the virtual unfolding method, and categorisation of folding techniques, could help researchers to understand this historical version of physical cryptography, while at the same time conserving their cultural heritage.

"This algorithm takes us right into the heart of a locked letter," the research team explains. "Sometimes the past resists scrutiny. We could simply have cut these letters open, but instead we took the time to study them for their hidden, secret, and inaccessible qualities. We've learned that letters can be a lot more revealing when they are left unopened. Using virtual unfolding to read an intimate story that has never seen the light of day—and never even reached its recipient—is truly extraordinary."

More information: *Unlocking history through automated virtual unfolding of sealed documents imaged by X-ray microtomography, Nature Communications (2021). DOI: 10.1038/s41467-021-21326-w*

http://bit.ly/3e9Qs3o

COVID Found Mutating Inside a Baby Born With The Virus, in a World First

Days after birth, baby's virus population changed and contained a mutated version of the virus along with the mother's virus strain

Mehreen Zaigham*

A pregnant woman with suspected COVID-19 was rushed by ambulance to Skåne University Hospital, in Malmo, Sweden, suffering from sudden severe abdominal pain. The doctors noticed that the unborn infant had an abnormally low heart rate, which can be a sign that the baby is not getting enough oxygen.

The doctors performed an emergency caesarean section and delivered the baby within minutes. Blood tests from the baby confirmed it had severely low oxygen, and throat swabs showed that both mother and baby were suffering from COVID.

Using throat swabs from the mother and the newborn, the genome of the virus was sequenced to confirm the possibility that the infant had been infected with COVID while still in the womb.

My colleagues and I – part of a study team at the hospital – found that the viral genome in the mother and the baby was identical. Since the baby had been isolated from the mother directly after the caesarean and had not come in contact with other family members when these tests were done, the findings confirmed that the baby was indeed infected before it was born.

However, a few days later, new genetic sequencing showed that the baby's virus population had changed and contained a mutated version of the virus along with the original virus strain from the mother. To the best of our knowledge, this is the first case of a genetic change of the coronavirus in the unique setting of mother-to-foetus transmission before birth.

Although it is common for viruses to mutate, this mutation (called A107G) happened just five days after the baby was delivered.

The genetic changes may have been stimulated by the baby coming in contact with the external environment outside the mother's womb. However, it was surprising how quickly this single mutation occurred.

The most important findings were the changes we saw in the placenta. The placenta takes blood and nutrients to the foetus and takes away waste and is critical for the growth and wellbeing of the foetus. We found that half the tissue was damaged.

There was widespread inflammation, and we found coronavirus protein on both the mother's and foetus's side of the placenta. We also found coronavirus protein in all areas that were damaged by inflammation.

The mother made a quick recovery from her COVID infection and was discharged four days after delivery, but the baby needed neonatal care since it was born prematurely (week 34 of pregnancy). The baby developed antibodies against the virus and had no severe symptoms after delivery. It was, therefore, the baby's own immune system that neutralised the virus as we did not find any antibodies in the mother's breast milk.

Rare but needs monitoring

Our study, which has just been published in *The British Journal of Obstetrics and Gynaecology*, is among only a handful of scientific papers that have investigated coronavirus transmission through the placenta.

Previous studies have reported rapid placental failure and abnormal foetal heart rhythm, similar to what we found. But with thousands of pregnant women infected worldwide, mother-to-baby transmission in the womb seems to be a rare complication of COVID during pregnancy.

Scientists think that this is because of the placental barrier that protects the baby in the womb from most infections. Also, the vital receptor needed for coronavirus entry into cells, called an ACE-2 receptor, only exists in low levels in the placenta.

In rare cases, coronavirus can damage the placenta – leading to a lack of oxygen in the unborn child – even if the mother has a mild case of COVID in late pregnancy.

Our findings suggest that perhaps we should rethink how we monitor pregnant women who have COVID, and they should be considered a more important risk group than we do today.

* *Postdoctoral Research Fellow, Obstetric & Gynecology, Skåne University Hospital, Lund University.*

http://bit.ly/3bdVE41

Researchers report new approach to cultured meat

Innovative laboratory biofabrication of bovine muscle tissue may help meet escalating future demands for dietary meat

Humans are largely omnivores, and meat has featured in the diets of most cultures. However, with the increasing population and pressure on the environment, traditional methods of meeting this fundamental food requirement are likely to fall short. Now, researchers at the University of Tokyo report innovative biofabrication of bovine muscle tissue in the laboratory that may help meet escalating future demands for dietary meat.

With global urbanization, the economics of animal husbandry are becoming unsustainable. From an environmental viewpoint, the land and water costs of modern mega-scale livestock farming are untenable, as are the greenhouse gas emissions and the overall toll on the planet. Additionally, there are ethical concerns against human exploitation of lower species for food.

To address future requirements, tissue engineering of cultured meat is under development at several centers worldwide. However, most biosynthetic meat products are amorphous or granular-like minced meat, lacking the grain and texture of real animal flesh. Mai Furuhashi, lead author, explains their novel process. "Using techniques developed for regenerative medicine, we succeeded in

culturing millimeter-sized chunks of meat wherein alignment of the myotubes help mimic the texture and mouthfeel of steak. For this, myoblasts drawn from commercial beef were cultured in hydrogel modules that could be stacked allowing fusion into larger chunks. We determined the optimal scaffolding and electrical stimulation to promote contractility and anatomical alignment of the muscle tissue to best simulate steak meat."

Researchers at The University of Tokyo develop a method of culturing meat in the laboratory in the form of millimeter-scale contractile beef muscle that closely simulates steak meat. **Credit: Institute of Industrial Science, the University of Tokyo**

Lead author Yuya Morimoto describes the synthesized product. "Our morphological, functional and food feature analyses showed that the cultured muscle tissue holds promise as a credible steak substitute. Breaking force measurements showed that toughness approached that of natural beef over time. Significantly, microbial contamination was undetectable; this has implications for cleanliness, consumer acceptability and shelf-life."

"Our method paves the way for further development of larger portions of realistic cultured meat that can supplement or replace animal sources," claims Shoji Takeuchi, senior and corresponding author. "However, there is a long way to go before lab-grown meat is indistinguishable from the real thing, and hurdles concerning consumer acceptance and cultural sensibilities are overcome. Nevertheless, this innovation promises to be a green and ethical alternative to animal slaughter in meeting our need for dietary meat." The article, "Formation of contractile 3-D bovine muscle tissue for construction of millimeter-thick cultured steak," was published in *Science of Food*.

More information: *Mai Furuhashi et al. Formation of contractile 3D bovine muscle tissue for construction of millimetre-thick cultured steak, npj Science of Food (2021).* DOI: 10.1038/s41538-021-00090-7

http://bit.ly/3uWdVej

Extinct atom reveals the long-kept secrets of the solar system

The unstable atom 92Nb, which has long since disappeared, provides information about the beginnings of our solar system.

by Peter Rüegg

Using the extinct niobium-92 atom, ETH researchers have been able to date events in the early solar system with greater precision than before. The study concludes that supernova explosions must have taken place in the birth environment of our sun.

If an atom of a chemical element has a surplus of protons or neutrons, it becomes unstable. It will shed these additional particles as gamma radiation until it becomes stable again. One such unstable isotope is niobium-92 (^{92}Nb), which experts also refer to as a radionuclide. Its half-life of 37 million years is relatively brief, so it went extinct shortly after the formation of the solar system. Today, only its stable daughter isotope, zirconium-92 (^{92}Zr), bears testimony to the existence of ^{92}Nb.

Yet scientists have continued to make use of the extinct radionuclide in the form of the ^{92}Nb-^{92}Zr chronometer, with which they can date events that took place in the early solar system some 4.57 billion years ago.

Use of the ^{92}Nb-^{92}Zr chronometer has hitherto been limited by a lack of precise information regarding the amount of ^{92}Nb that was present at the birth of the solar system. This compromises its use for dating and determining the production of these radionuclides in stellar environments.

Meteorites hold the key to the distant past

Now a research team from ETH Zurich and the Tokyo Institute of Technology (Tokyo Tech) has greatly improved this chronometer.

The researchers achieved this improvement by means of a clever trick: they recovered rare zircon and rutile minerals from meteorites that were fragments of the protoplanet Vesta. These minerals are considered to be the most suitable for determining ^{92}Nb, because they give precise evidence of how common ^{92}Nb was at the time of the meteorite's formation. Then, with the uranium-lead dating technique (uranium atoms that decay into lead), the team calculated how abundant ^{92}Nb was at the time the solar system's formation. By combining the two methods, the researchers succeeded in considerably improving the precision of the ^{92}Nb-^{92}Zr chronometer.

"This improved chronometer is thus a powerful tool for providing precise ages for the formation and development of asteroids and planets—events that happened in the first tens of millions of years after the formation of the solar system," says Maria Schönbächler, Professor at the Institute of Geochemistry and Petrology at ETH Zurich, who led the study.

Supernovas release niobium-92

Now that the researchers know more precisely how abundant ^{92}Nb was at the very beginnings of our solar system, they can determine more accurately where these atoms were formed and where the material that makes up our sun and the planets originated.

The research team's new model suggests that the inner solar system, with the terrestrial planets Earth and Mars, is largely influenced by material ejected by Type Ia supernovae in our Milky Way galaxy. In such stellar explosions, two orbiting stars interact with each other before exploding and releasing stellar material. In contrast, the outer solar system was fed primarily by a core-collapse supernova—probably in the stellar nursery where our sun was born –, in which a massive star collapsed in on itself and exploded violently.

More information: *Makiko K. Haba et al. Precise initial abundance of Niobium-92 in the Solar System and implications for p-process nucleosynthesis, Proceedings of the National Academy of Sciences (2021).* [*DOI: 10.1073/pnas.2017750118*](https://doi.org/10.1073/pnas.2017750118)

[***http://bit.ly/3c04d1B***](http://bit.ly/3c04d1B)

Requests for brand name over generic prescription drugs cost the Medicare program $1.7 billion in a single year, study finds

Opting for generic over brand name prescription drugs would save hundreds of millions a year

The Medicare Part D program would have saved $977 million in a single year if all branded prescription drugs requested by prescribing clinicians had been substituted by a generic option, according to a new study by researchers at the Johns Hopkins Bloomberg School of Public Health. And if Medicare patients had requested generic drugs instead of brand name drugs, the Medicare Part D program would have saved an additional $673 million in one year, for a total savings of $1.7 billion.

Medicare Part D offers supplemental outpatient drug coverage plans for seniors age 65 and older and people receiving disability benefits, and accounts for approximately one-third of total prescription drug spending in the U.S.

Despite laws in all 50 states and the District of Columbia promoting generic drug dispensing, the study found that in 2017 under the Medicare Part D program, prescribing clinicians and patients together requested brand name prescription drugs over generics 30 percent of the time when a brand name drug was dispensed.

Among the 169 million filled prescriptions analyzed in the study, 8.5 million involved dispensing a brand-name prescription drug when generics were available. Of these, 17 percent (1.4 million claims) involved the prescribing provider requesting a brand-name drug over a generic version and, in another 13.5 percent (1.1 million claims) patients requesting brand name drugs versus generic options. The study will be published online March 2 in JAMA Network Open.

"Even with laws in place, requesting a brand name drug happens way more frequently than it should," says Gerard Anderson, PhD, professor in the Department of Health Policy and Management at the Bloomberg School. "This dispensing pattern results in exponentially higher costs for both the Medicare Part D program and patients."

For the study, the researchers analyzed Medicare Part D prescription drug claims from 2017. The analysis drew from a random sample representing 20 percent of Medicare beneficiaries and 224 drugs that had at least one generic substitute and at least 1,000 claims. The researchers analyzed information from each claim, including the type of drug dispensed, Medicare Part D spending, and the patient out-of-pocket spending.

Medicare patients would also benefit by paying less for prescriptions drugs. The study found that Medicare patients would have saved $161 million in 2017 if prescribing providers had requested generic drugs over brand name options. In addition, Medicare patients would have also saved $109 million if patients had requested generic drugs over brand name options. In all, Medicare patients spent $270 million more than necessary for prescriptions drugs in the year studied.

While branded prescription drug dispensing accounts for only 5 percent of Medicare Part D drug claims when both brand and generic drugs are available, these findings underscore how costly brand name drugs are to Medicare beneficiaries and the Medicare program.

Recent research has found that skepticism about generic medications is common among clinicians and patients. Surveys have found that more than one-third of patients reported a preference for branded products to generics, and 46 percent of patients asked their provider to prescribe a brand name drug over a generic.

The study also found that in 2017 the Medicare Part D program spent a total of $4.42 billion on brand name prescription drugs where no specific drug selection was indicated by a clinician or pharmacist. The authors recommend that the Medicare program look into these open-ended prescriptions, to see if it can reduce expenditures by encouraging opting for generic over brandname drugs when available.

The findings suggest that policies targeting both the clinician and the patient could have the greatest potential to promote generic drug use and therefore cost savings. Improving clinicians' perception of generic medication, raising awareness of the availability of generic drugs, and limiting direct pharmaceutical marketing can have substantial influence over the patients' medication preferences.

"Patients should always be mindful of the extra costs for themselves and for taxpayers associated with requesting a brand-name prescription drug," says Ge Bai, PhD, CPA, associate professor at the Johns Hopkins Carey Business School and in the Bloomberg School's Department of Health Policy and Management. "Prescribing clinicians can also play an important role in educating their patients on the safety and effectiveness of generic drugs."

"Factors Associated with Prescriptions for Branded Medications in the Medicare Part D Program" was written by Mariana Socal, Ge Bai, and Gerard Anderson.

The study was supported by Arnold Ventures.

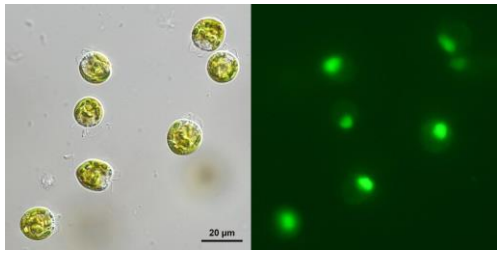
http://bit.ly/3ejY8zM

Littlest shop of horrors: Hungry green algae prefer to eat bacteria alive

New study points to potential widespread phagocytosis among green algae, suggests improved methodology in environmental microbiology

New research suggests that the ability of green algae to eat bacteria is likely much more widespread than previously thought, a finding that could be crucial to environmental and climate science. The

work, led by scientists at the American Museum of Natural History, Columbia University, and the University of Arizona, found that five strains of single-celled green algae consume bacteria when they are "hungry," and only when those bacteria are alive. The study is published today in The *ISME Journal*.



A brightfield image of Pyramimonas parkeae (left) and a green fluorescence image of the same algae, revealing the ingested bacteria inside the cells (right). **Credit: N. Bock & E. Kim**

"Traditionally, we think of green algae as being purely photosynthetic organisms, producing their food by soaking in sunlight," said Eunsoo Kim, an associate curator at the American Museum of Natural History and one of the study's corresponding authors. "But we've come to understand that there are potentially a number of species of green algae that also can eat bacteria when the conditions are right. And we've also found out just how finicky they are as eaters."

In 2013, Kim and her colleagues were the first to provide definitive proof that green algae eat bacteria, which they showed in an alga from the genus Cymbomonas. While some in the field viewed this behavior as a rare exception, Kim's lab continued to explore whether mixotrophy--the term that describes the mode by which organisms use both photosynthesis and phagocytosis (cell-eating) to power themselves--existed in other types of green algae. It was a difficult behavior to confirm until the research team came up with a new experimental approach led by Nicholas Bock, a graduate student at Columbia University's Lamont-Doherty Earth Observatory, and Museum postdoctoral researcher Sophie Charvet.

The researchers conducted feeding experiments with live bacteria that were labeled with a non-toxic fluorescent dye and combined the bacteria with five different strains of unicellular green algae called prasinophytes for analyses through a flow cytometer, which helps scientists analyze cell properties in solution. The flow cytometer measured increasing levels of green fluorescence in the algal cells over time, suggesting that the algae were consuming the glowing bacteria. To confirm that ingestion was actually occurring, the researchers used high-precision microscopy to pinpoint the origin of the green fluorescence to the interior of the algal cells. In the process, the team discovered two particular quirks about the finicky eaters: the algal strains they tested only ate live bacteria (dead bacteria in the experiments were left untouched), and they ate more when the levels of other nutrients were low. These findings have large implications for the environmental study of green algae.

"Traditionally when people study bacterial ingestion by algae in the oceans for environmental samples, they use fluorescently labeled bacteria that have been killed in the labeling process," Charvet said. "At least for the five algal strains we had in culture, they preferentially feed on the live bacteria and seem to be snubbing the killed bacteria. This means that the impact of algae on bacterial communities in their natural environment has possibly been underestimated drastically because of the methods used."

Green algae are found around the world and help form the foundation of the aquatic food web. Along with other photosynthetic organisms like cyanobacteria, diatoms, and dinoflagellates--which are given the umbrella term phytoplankton--green algae function as a sort of biological carbon pump, consuming carbon dioxide on a scale equivalent to trees and other land plants in terrestrial ecosystems.

"For decades, scientists have been able to send satellites up and get optical data to infer global distributions of phytoplankton via chlorophyll measurement," said Bock, who conducted the work at Columbia under Solange Duhamel, now at the University of

Arizona, Tucson. "Through that, we've come to understand that phytoplankton are vitally important for carbon cycling. The assumption in all of this is that all that chlorophyll just represents photosynthesis. It doesn't account for the mixotrophy piece because there's no easy way to detect [via satellite] if they're eating other cells. Our findings highlight that the story is actually more complex."

In parallel to the experiments led by Bock and Charvet, green algal bacteria-eating was investigated using a gene-based prediction model formulated by John Burns from the American Museum of Natural History and the Bigelow Laboratory for Ocean Sciences. The predictions agreed with the experimental results and suggested that the behavior is even more widespread among the green algal tree of life.

Other authors of this work include Yangtsho Gyaltshen from the American Museum of Natural History and Andrey Rozenberg from the Israel Institute of Technology.
This work was supported in part by the U.S. National Science Foundation no.s CAREER-1453639, OCE-14580950, and OCE-1458070, and the Simons Foundation grant no. 382790. Study DOI: 10.1038/s41396-021-00899-w

http://bit.ly/2PDUGWF

Vaccine shows signs of protection against dozen-plus flu strains

Candidate outperforms commercial vaccine, bolsters promise of universal vaccine for humans

Ask Eric Weaver about pandemics, and he's quick to remind you of a fact that illustrates the fleeting nature of human memory and the proximal nature of human attention: The first pandemic of the 21st century struck not in 2019, but 2009.

That's when the H1N1/09 swine flu emerged, eventually infecting upwards of 1.4 billion people -- nearly one of every five on the planet at the time. True to the name, swine flus jump to humans from pigs. It's a phenomenon that has been documented more than 400 times since the mid-2000s in the United States alone.

"They're considered the great mixing vessel," said Weaver, associate professor of biological sciences at the University of Nebraska-Lincoln. "They're susceptible to their own circulating influenzas, as well as many of the avian and human influenzas.

"If you put an avian, a swine and a human virus into the same cell, they can swap genome segments. When you mix those viruses in the swine, what pops out could be all swine, or a little human and swine, or a little avian and swine, or a little of all three. And you never know: You might get the perfect combination of parts that makes for a very high-fitness virus that is highly transmissible and new to humans, meaning that people don't have immunity to it."

All of it helps explain why Weaver has spent years researching how to develop a vaccine that protects against as many strains of influenza as possible, including those that have yet to emerge. In a new study, Weaver, doctoral candidate Brianna Bullard and colleagues have debuted the results of an approach that demonstrates promising signs of protection against more than a dozen swine flu strains -- and more than a leading, commercially available vaccine.

"This is the best data I've ever seen in the (research) literature," Weaver said of the team's findings, recently published in the journal *Nature Communications*.

The "H" and "N" in H1N1 refer to two crucial proteins, hemagglutinin and neuraminidase, that reside on the surface of influenza viruses and allow them to enter and exit cells. But it's the H3 subtype of influenza -- H3N2, specifically -- that has accounted for more than 90% of swine-to-human infections in the United States since 2010, making it the target of Weaver's most recent research.

In his efforts to combat multiple strains of swine H3N2, Weaver employed a computational program, Epigraph, that was co-developed by Bette Korber of Los Alamos National Laboratory.

The "epi" is short for epitope: the bit of a viral protein, such as hemagglutinin, that draws the attention of an immune system. Any one epitope, if administered as a vaccine, will stimulate an immune response against only a limited number of closely related viral strains.

So Weaver put Epigraph to work analyzing data on every known and available mutational variant of hemagglutinin, which it then used to predict which collection of epitopes would grant immunity against the broadest, most diverse range of strains. Those hemagglutinin proteins are usually composed of around 560 amino acids, whose type and sequence determine the structure and function of the epitopes.

Starting at the start of an amino acid string, Epigraph analyzed the sequence of amino acids No. 1 through No. 9 before sliding down to analyze Nos. 2-10, then 3-11, and so on. After doing the same for every epitope, the program determined the most common nine-acid sequences from the entire batch -- the entire catalogue of known H3N2 strains in pigs.

"So what you end up with are the most common epitopes that exist in nature linked together, then the second-most common, and then the third-most common," Weaver said. "When you look at it from an evolutionary standpoint, the first resembles what most of the viruses look like. The second starts to look a bit different, and the third looks even more different.

"But all three of these make a contribution to the vaccine itself, and they work through slightly different mechanisms."

When testing the resulting three-epitope cocktail in mice and pigs, the team found that it yielded immune response signatures and physiological protection against a much wider variety of strains than did FluSure, a commercial swine vaccine.

In mice, the team tested its vaccine against 20 strains of swine-derived H3 flu. The vaccine generated clinically relevant concentrations of antibodies -- the molecules that neutralize a virus before it enters a cell -- against 14 of those 20 strains. FluSure managed the same feat against just four of the 20.

A separate experiment presented the mice with four strains that represented a cross-section of H3 diversity. In all four cases, Epigraph-vaccinated mice produced notable levels of T-cells, which, among other responsibilities, instruct infected cells to die for the sake of avoiding further viral transmission. FluSure-vaccinated mice, by contrast, showed little T-cell response to any of the four strains.

Those cellular-level responses appeared to scale up, too. When challenged with flu viruses, Epigraph-vaccinated mice generally lost less weight, and exhibited fewer viral particles in the lungs, than did their FluSure-vaccinated counterparts. And when mice were challenged with a lethal H3 strain derived from humans, only the Epigraph vaccine protected all of the specimens that received it.

That performance carried over to pigs. Cells taken from swine injected with just one dose of the Epigraph vaccine produced substantial antibodies in response to 13 of 20 H3 strains, including 15 of 16 that originated in North America or were derived from humans.

A single dose of FluSure, meanwhile, generated significant antibodies against none of the 20. Though a second dose of FluSure did elevate those antibody concentrations, they remained about four times lower, on average, than the Epigraph-induced responses. T-cell responses, too, remained higher in Epigraph-vaccinated pigs.

More, and more-generalizable, experiments will be needed to verify the Epigraph vaccine's performance, Weaver said. For one, the team is looking to test whether the vaccine candidate generates actual immunity in living pigs, beyond the promising immune responses from their cells in a lab. There's also the matter of determining how long any immunity might last.

But Weaver has already developed a human equivalent of the swine flu vaccine cocktail that he's likewise preparing to test. Considering the similarities between flu infections in humans and pigs -- susceptibilities to subtypes, clinical symptoms, even viral receptors in respiratory tracts -- he said the recent findings bode well for those future, human-centric efforts. Success on that front could eventually mean pivoting away from the current approach to flu vaccinations, whereby virologists are forced to predict which strains will dominate a flu season -- and, despite their best efforts, sometimes miss the mark.

"This study is equivalent to a bench-to-bedside study, where the positive results in the preclinical mouse study are confirmed by positive results in a clinical pig study," Weaver said. "This gives us confidence that when the concept is applied to human influenza virus, we'll see the same translation from preclinical studies to clinical studies in humans."

Weaver, Bullard and Korber authored the Nature Communications study with Brigette Corder, doctoral student at Nebraska, along with Richard Webby, Jennifer DeBeauchamp and Adam Rubrum of St. Jude Children's Research Hospital. The team received support from the National Institutes of Health.

http://bit.ly/3uXsfDa

Sesaminol: Parkinson's disease's surprise medicine

Osaka City University shows that sesaminol, purified from industrial sesame seed by-product, can help prevent Parkinson's disease.

Sesame seed oil, used by many for its nutty aroma and high burn-point, is made by extracting the fatty oils from sesame seeds, with the empty shells thrown out as waste. In a literal instantiation of the age-old adage "one man's trash is another man's treasure", researchers discovered that a chemical called sesaminol, abundant in this waste, has protective effects against Parkinson's disease.

"Currently there is no preventive medicine for Parkinson's disease", states OCU Associate Professor Akiko Kojima-Yuasa, "we only have coping treatments". Associate Professor Kojima-Yuasa led her research group through a series of experiments to understand the effects of sesaminol on *in vitro* and *in vivo* Parkinson's disease models.

Parkinson's disease is caused when certain neurons in the brain involved with movement break down or die due in part to a situation called oxidative stress - neurons in the brain come under extreme pressure from an imbalance between antioxidants and reactive oxygen species (ROS). The team found in cell-based *in vitro* experiments that sesaminol protected against neuronal damage by promoting the translocation of Nrf2, a protein involved in the response to oxidative stress, and by reducing the production of intracellular ROS.

In vivo experiments brought Associate Professor Kojima-Yuasa's team equally promising results. The impairment of movement due to Parkinson's disease is the result of damaged neurons producing less dopamine than is naturally needed. The team showed that mice with Parkinson's disease models show this lack of dopamine production. However, after feeding the mice a diet containing sesaminol for 36 days, the research team saw an increase in dopamine levels. Alongside this, a rotarod performance test revealed a significant increase in motor performance and intestinal motor function.

With the first-ever medicine for Parkinson's disease potentially being the naturally occurring food ingredient sesaminol, and this ingredient being found in the naturally occurring waste of the sesame seed industry, Associate Professor Kojima-Yuasa and her team are ready to take their work to the clinical trial phase and connect the consumption/production chain in a way that, as she puts it, "prevents diseases with natural foods to greatly promote societal health."

http://wb.md/3v247zw

A Patient Insisted on a Trial. Docs Listened and Saved Lives

An Unimaginable Result, Says Trialist

Nick Mulcahy

Powerful things can happen when clinicians and researchers listen to patients — that's the main takeaway message from a recent viral Twitter thread that was repeatedly described as "amazing," "incredible," "beautiful," and "inspiring" by readers, including many healthcare professionals.

The 15-part tweet thread tells a story from nearly 20 years ago of what may be an unprecedented event in oncology: a patient-conceived clinical trial. The study set out to evaluate reducing the dose of a drug with notorious toxicity, but unexpectedly ended up saving lives.

"The result was wilder than anyone could have imagined," sums up trial investigator Vincent Rajkumar, MD, of the Mayo Clinic, Rochester, Minnesota, in comments to *Medscape Medical News*.

Rajkumar, an expert in the treatment of multiple myeloma, recalls how in the early 2000s, there was an upswing in the development of new drugs for the incurable blood cancer.

In 2002, he had just completed a clinical trial demonstrating that thalidomide, infamous for causing birth defects, was significantly effective as initial treatment in early-stage multiple myeloma.

Those results were subsequently used to secure US Food and Drug Administration approval of thalidomide for myeloma. It was the first new drug that showed single-agent efficacy for myeloma in three decades.

"As a young investigator, I was thrilled with the success and eager for the next exciting trial testing fancy new regimens," Rajkumar writes in the Twitter thread.

"But a patient with myeloma, Mike Katz, had other ideas," he continues.

Katz "had battled myeloma for years and knew all of the recent advances. More importantly he attended numerous patient support group meetings and had his finger on the pulse of what myeloma patients were going through," Rajkumar writes.

A New York City resident, Katz served as the patient advocate on the Eastern Cooperative Oncology Group's (ECOG's) myeloma committee, part of the clinical trials network of the National Cancer Institute (NCI).

Katz, who died of the disease 6 years ago, "was just trying to survive" in addition to doing the selfless work of an advocate, which became "a mission," says his son, Jason.

The Next Big Trial

In 2002, the ECOG committee, including Katz and Rajkumar, gathered and considered ideas for their next big trial.

Rajkumar recalls that "while docs talked about creating 'exciting' combinations, Mike said, 'Listen, what patients really want is freedom from the side effects of dexamethasone. All these new drugs don't help if patients cannot take them. You guys are giving too much dexamethasone. And people are suffering,' " he said.

At the time, myeloma patients were regularly treated with high-dose dexamethasone in regimens of nearly 500 mg monthly.

The side effects of the steroid include blood clots as well as a long list of physical and mental symptoms, such as blurred vision, weight gain, agitation, irritability, and mood changes.

David Mitchell, of Bethesda, Maryland, who has had myeloma for more than 10 years, relates how the steroid feels at high doses. "You get a big steroid ride and you feel great. But then you crash. You can't sleep at all and it starts to mess with your mind."

Mitchell describes "crying jags, deep fits of depression and the jitters.... It was bad. It was ugly. I was doing things like yelling at

the dog. I thought I was going crazy."

Then, in a moment of desperation, he called a myeloma hotline, where a nurse asked him: "Has anyone told you about dexamethasone psychosis?"

Mood-related side effects also dogged Mike Katz, says his son. "Steroids took a toll on him," Jason comments about his father. "At times, it was awful. He really got on edge."

Mitchell, who is founder of the nonprofit organization, Patients for Affordable Drugs, summarizes the "dex" experience: "Everyone hates it."

Important Component of Therapy?

Rajkumar explains that for myeloma, dexamethasone was administered at high doses to kill cancer cells: "It was an important component of therapy."

But at the ECOG committee meeting, "Mike disagreed," he adds.

Katz explained his thinking to the committee: "You are giving dexamethasone at a high dose on the basis that this is how it has always been done. Please run a trial and see if in the era of new drugs you still need such high doses of dexamethasone."

Committee members were "skeptical" about Katz's vision, says Rajkumar.

We had waited 40 years for new drugs and Mike wants us to test Dex dosing! Dr Vincent Rajkumar

"But Mike was not going to give up," he adds.

"[Mike] insisted we do a randomized trial of high dose dexamethasone versus low dose dexamethasone. To us the idea seemed destined to fail. It seemed so boring. We had waited 40 years for new drugs and Mike wants us to test Dex dosing!" writes Rajkumar in one of his tweets.

But Katz, who had an MBA and worked as a management consultant, was calm, convincing, and fearless, Rajkumar says.

"We respected Mike. We knew he was aware of what patients were going through. We saw 100-200 myeloma patients a year. He interacted with thousands," he writes.

The committee eventually convinced the NCI and ECOG leadership that testing to determine the optimal dose of dexamethasone was "the most important publicly funded randomized trial.... It wasn't easy. But we got it approved," says Rajkumar.

The gambit was quickly vindicated: the trial accrued patients faster than any myeloma trial ever among national cooperative groups.

A Stunning Result

The trial to test high-dose vs low-dose dexamethasone was designed as a noninferiority study with an expected benefit of reduced adverse events. But it produced a stunning surprise and was stopped early.

"Deaths with high-dose dexamethasone (control, standard of care arm) were significantly higher than with low-dose dexamethasone!" Rajkumar declares in the Twitter thread.

"We had hypothesized that by using low-dose dexamethasone we would have less toxicity and similar efficacy. Little did we know that just a change in Dex dose would save lots of lives: At one year 96% were alive with low dose Dex versus 87% with high dose standard of care Dex," he continues.

The 2-year overall survival rate was even more impressive: 87% with low-dose, vs 75% with high-dose dexamethasone.

In addition, all serious side effects, including blood clots, infections, and fatigue, were reduced with low-dose dexamethasone.

In the pivotal trial, patients in the high-dose group received dexamethasone 40 mg on days 1–4, 9–12, and 17–20 of a 28-day cycle (total, 480 mg); patients in the low-dose group received dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle (total dose, 160 mg).

Both arms of the study included lenalidomide (*Revlimid*) 25 mg on days 1–21 of the cycle. An analogue of thalidomide, lenalidomide

was still experimental in 2002. It would go onto become a billion-dollar-a-year drug for its maker, Celgene.

Lenalidomide plus low-dose dexamethasone is now the backbone of most myeloma regimens, points out Rajkumar. "The lower dose of Dex has allowed us to build many 3-4 drug combinations. We are indebted to Mike. We grieve his loss," he adds.

Katz's "legacy and work...endures," says Rajkumar, who notes that the trial, published in *The Lancet Oncology* in 2010, is one of the most cited myeloma articles ever.

The American Society of Clinical Oncology honored Katz in 2014 with the Partners in Progress Award at the group's annual meeting. Son Jason says it was "one of the greatest achievements of his life."

Myeloma patient Mitchell says he "owes a great debt of gratitude" to Katz.

Ten years ago, after learning about dexamethasone psychosis, Mitchell contacted his oncologist, who had just read about the trial results. He cut Mitchell's dosage immediately.

"I literally benefitted from this man's effort.... This was a huge thing because it dramatically affected my quality of life," comments Mitchell, who is now on a low-dose regimen (12 mg weekly) of the steroid, along with three other drugs.

Listening to Patients

Last month, Rajkumar's Twitter thread about this story was a viral hit, with 305,000 impressions (the number of people who saw the initial tweet), 4000 likes, 1100 retweets, and 430 comments.

"Dr Rajkumar is a great storyteller," says Jason Katz.

"This story is amazing. And dex is the worst," tweeted Lianne Kraemer, who lives with metastatic breast cancer and is a patient advocate. Many other people also described the story as "amazing," including David Lewis, MD, of Brown University, in Providence Rhode Island, Marclebio Dourado, MD, PhD, of the University of Pernambuco, in Receife, Brazil, and Suzie Peat, MD, of the National Health Service in the United Kingdom.

Many readers emphasized the importance of listening to patients. "Truly powerful. Listening to patients and their advocates leads to advances and patient centered care," tweeted Benjamin Parsons, MD, of Gunderson Health System, in La Crosse, Wisconsin.

"I give a lot of credit to these doctors for listening," says Mitchell.

Others encouraged the practice of medicine to continue to evolve toward the patient experience. "It is REALLY time that we woke up to Patient Reported Outcome Measures, Patient Experience of Care," tweeted Tejal Lathia, MD, of BYL Nair Charitable Hospital, Mumbai, India.

The NCI facilitates patient and patient advocate involvement in clinical trials development. Every NCI-funded cooperative group, including ECOG, has its own patient advocate committee.

At the SWOG Cancer Research Network, "patient advocates weigh in on every trial as it is developed and executed," says Wendy Lawton, the group's director of media relations. The network has 28 advocates, including five people of color, a military veteran, and two adolescent and young adult advocates.

Rick Bangs, SWOG patient advocate chair and a bladder and prostate cancer survivor from Pittsford, New York, says advocates have modified study designs through requests such as removing placebo arms, adding excluded subpopulations, and reducing doses.

Nevertheless, the fact that cancer patient Mike Katz conceived of the low-dose dexamethasone trial may be unique in oncology research.

"You can make discoveries if you listen," says Rajkumar.

Rajkumar, Mitchell, and Jason Katz have disclosed no relevant financial relationships.

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http://bit.ly/3qqgvW9

Prehistoric killing machine exposed

Previously thought of as heavy, slow and sluggish, the 260-million-year-old predator, Anteosaurus, was a ferocious hunter-killer.

Judging by its massive, bone-crushing teeth, gigantic skull and powerful jaw, there is no doubt that the Anteosaurus, a premammalian reptile that roamed the African continent 265 to 260 million years ago—during a period known as the middle Permian—was a ferocious carnivore.

However, while it was previously thought that this beast of a creature—that grew to about the size of an adult hippo or rhino, and featuring a thick crocodilian tail—was too heavy and sluggish to be an effective hunter, a new study has shown that the Anteosaurus would have been able to outrun, track down and kill its prey effectively.

Despite its name and fierce appearance, Anteosaurus is not a dinosaur but rather belongs to the dinocephalians—mammal-like reptiles predating the dinosaurs. Much like the dinosaurs, dinocephalians roamed and ruled the Earth in the past, but they originated, thrived, and died about 30 million years before the first dinosaur even existed.

The fossilized bones of Dinocephalians are found in many places in the world. They stand out by their large size and heavy weight. Dinocephalian bones are thick and dense, and Anteosaurus is no exception. The Anteosaurus' skull was ornamented with large bosses (bumps and lumps) above the eyes and a long crest on top of the snout which, in addition to its enlarged canines, made its skull look like that of a ferocious creature. However, because of the heavy architecture of its skeleton, it was previously assumed that it was a rather sluggish, slow-moving animal, only capable of scavenging or ambushing its prey, at best.

"Some scientists even suggested that Anteosaurus was so heavy that it could only have lived in water," says Dr. Julien Benoit of the Evolutionary Studies Institute at the University of the Witwatersrand (Wits University).

By carefully reconstructing the skull of the Anteosaurus digitally using X-ray imaging and 3-D reconstructions, a team of researchers investigated the internal structures of the skull and found that the specific characteristics of its brain and balance organs were developed in such a way that it was everything but slow-moving.

"Agile predators such as cheetahs or the infamous Velociraptor have always had a very specialized nervous systems and fine-tuned sensory organs that enable them to track and hunt down prey effectively," says Benoit. "We wanted to find out whether the Anteosaurus possessed similar adaptations."

***A live reconstruction of Anteosaurus attacking a herbivorous Moschognathus*. Credit: Alex Bernardini (@SimplexPaleo)**

The team found that the organ of balance in Anteosaurus (its inner ear) was relatively larger than that of its closest relatives and other contemporaneous predators. This indicates that Anteosaurus was capable of moving much faster than its prey and competitors. They also found that the part of the brain responsible for coordinating the movements of the eyes with the head was exceptionally large, which would have been a crucial trait to ensure the animal's tracking abilities.

"In creating the most complete reconstruction of an Anteosaurus skull to date, we found that overall, the nervous system of Anteosaurus was optimized and specialized for hunting swiftly and striking fast, unlike what was previously believed," says Dr. Ashley

Kruger from the Natural History Museum in Stockholm, Sweden and previously from Wits University.

"Even though Anteosaurus lived 200-million years before the famous dinosaur Tyrannosaurus rex, Anteosaurus was definitely not a 'primitive' creature, and was nothing short of a mighty prehistoric killing machine," says Benoit.

The study is published in *Acta Palaeontologica Polonica*.

http://bit.ly/3sO5YG6

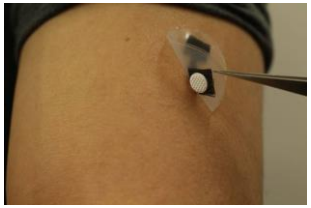
This patch developed in Japan could let you vaccinate yourself

People may one day be able to vaccinate themselves against maladies simply by applying a patch to their skin

by Eriko Yamakuma

Nations worldwide are now scrambling to find staff to administer COVID-19 vaccinations amid a shortage of front-line medical workers.

But new research from Japan shows that people may one day be able to vaccinate themselves against maladies — from the coronavirus to the flu — simply by applying a patch to their skin that allows the vaccine to be absorbed into the body quicker than with conventional medical patches.



The patch uses low-voltage electricity, allowing an array of porous microneedles on the patch to administer more of the drug into the skin, and faster. **| Matsuhiko Nishizawa**

In a study published in Nature Communications, a British scientific journal, in January, Matsuhiko Nishizawa, a professor at Tohoku University, and his research team developed a “biobattery-powered microneedle patch” that allows a vaccine to be absorbed faster than with the patches currently available commercially.

“In the future, we want people to administer the novel coronavirus vaccines and other kinds of vaccines on their own,” Nishizawa said. “I am doing the best I can for this technology to be used for COVID-19 vaccinations.”

Conventional microneedle patches, which have already been commercialized for migraine treatments and pain relief, allow a limited dosage to be injected, and the drugs take longer to pass through the skin.

Nishizawa’s team, however, improved on those aspects using low-voltage electricity, allowing an array of porous microneedles on the patch to administer more of the drug into the skin, and faster.

The electricity is powered by a biofuel cell, a technology developed by the same research group that generates electricity on the skin surface using enzymes.

Although it may take years to get government approval for applying the technology to vaccines, Nishizawa hopes it will be used for a COVID-19 vaccine in the future. For now, the more realistic application would allow patients to treat themselves with certain drugs at home.

Its organic composition, combined with the biofuel cells, means the patch can potentially be used for vaccinations in nations with an unstable or limited electricity supply, as well as areas hit by disaster.

http://bit.ly/3v1lFeZ

Woman's foul-smelling 'turkey ear' caused by decades-long infection

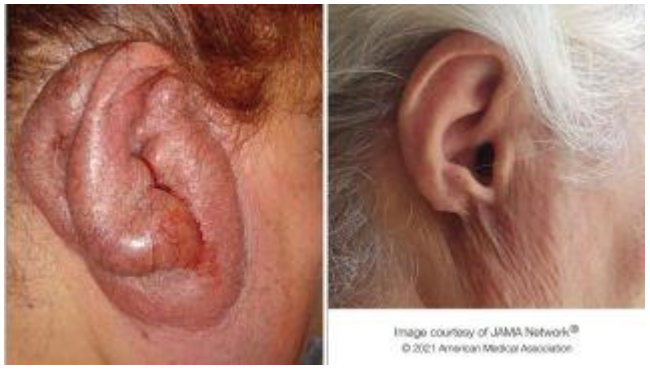
A tuberculosis infection of the skin caused her right ear to progressively swell over many years

By Nicoletta Lanese - Staff Writer

A woman in her 50s was diagnosed with a case of "turkey ear," in which a tuberculosis infection of the skin caused her right ear to progressively swell over many years until it reached an enormous size. The term turkey ear specifically refers to an infection of the earlobe that causes the skin to turn reddish, bumpy and hard to the touch; the comparison to turkeys may be a reference to the birds'

fleshy, bumpy necks, but the case reports don't specify which feature inspired the name.

In the woman's case, the infection started in childhood and slowly progressed over time, turning the swollen ear a reddish-brown color, according to a report of the case published March 3 in the journal JAMA Dermatology.



A woman in her 50s had a case of "turkey ear" (left) that had slowly progressed since her childhood. After treatment, the infection resolved, leaving a scar (right). **(Image credit: JAMA Network, 2021 American Medical Association)**

An examination, conducted at a medical center in Israel, also revealed that regions of the woman's ear had taken on an "apple jelly appearance," literally meaning that the color resembled that of a jelly made from cooked apples, the authors wrote. The term "apple jelly" also refers to the texture of the raised nodules of infected skin, which feel gelatinous when touched, according to a 2013 report in the journal Infectious Diseases in Clinical Practice.

"She was adamant that the lesion had been present since early childhood but had gradually increased" and had begun to leak a foul-smelling discharge, the authors wrote.

The woman originally went to the clinic in 2008 and received two months of treatment with four antibiotic medications for the turkey ear; the treatment was then cut back to two medications for the following seven months. The infection had been improving with treatment, but she did not follow up until 2020, when doctors had a chance to reexamine her, the authors wrote. Her infection had completely resolved, and the ear had shrunk back to a normal size. Only a patch of scarred skin remained as a mark of the infection.

Tuberculosis infections of the skin are caused by the same bacterium that infects the lungs, known as *Mycobacterium tuberculosis*, according to the case report. It's relatively rare for the bacterium to infect the skin, though, as compared with other infection sites outside the lungs, such as the lymph nodes, according to a 2012 report in the Indian Journal of Dermatology.

Specifically, the woman with turkey ear was diagnosed with "lupus vulgaris," a condition in which the *M. tuberculosis* infection progresses very slowly in the skin, changing its color and texture over the course of several years. This is the most common manifestation of tuberculosis infection in the skin.

The infection usually occurs when *M. tuberculosis* migrates to the skin from elsewhere in the body, often via the blood or lymphatic system. Very, very rarely, the condition can set in after a person receives the Bacillus Calmette-Guérin (BCG) vaccine, intended to prevent tuberculosis, the authors noted. This unusual complication is estimated to occur in only 5 out of every 1 million of these vaccinations, according to a 2016 report in the journal Case Reports in Dermatology.

The BCG vaccine is not widely used in the United States, where control measures have effectively reduced the risk of infection, but the vaccine is still commonly given to infants and children in countries where the condition remains common, according to the Centers for Disease Control and Infection (CDC).

"The chronic, relatively asymptomatic nature of [lupus vulgaris] may cause a significant delay in diagnosis," the authors noted. In fact, the authors found several other case reports describing patients who had lupus vulgaris for decades before being diagnosed.

In general, tuberculosis of the skin has "become rare in past decades," but the disease could still crop up in unexpected places as

people emigrate from regions where tuberculosis is endemic, the authors wrote. Therefore, dermatologists worldwide should still consider lupus vulgaris as a possibility if they encounter patients with turkey ears or apple jelly nodules, they wrote.

http://bit.ly/3kQiK49

Original error

Retracing the history of the mutation that gave rise to cancer decades later

There is no stronger risk factor for cancer than age. At the time of diagnosis, the median age of patients across all cancers is 66. That moment, however, is the culmination of years of clandestine tumor growth, and the answer to an important question has thus far remained elusive: When does a cancer first arise?

At least in some cases, the original cancer-causing mutation could have appeared as long as 40 years ago, according to a new study by researchers at Harvard Medical School and the Dana-Farber Cancer Institute.

Reconstructing the lineage history of cancer cells in two individuals with a rare blood cancer, the team calculated when the genetic mutation that gave rise to the disease first appeared. In a 63-year-old patient, it occurred at around age 19; in a 34-year-old patient, at around age 9.

The findings, published in the March 4 issue of *Cell Stem Cell*, add to a growing body of evidence that cancers slowly develop over long periods of time before manifesting as a distinct disease. The results also present insights that could inform new approaches for early detection, prevention, or intervention.

"For both of these patients, it was almost like they had a childhood disease that just took decades and decades to manifest, which was extremely surprising," said co-corresponding study author Sahand Hormoz, HMS assistant professor of systems biology at Dana-Farber.

"I think our study compels us to ask, when does cancer begin, and when does being healthy stop?" Hormoz said. "It increasingly appears that it's a continuum with no clear boundary, which then raises another question: When should we be looking for cancer?"

In their study, Hormoz and colleagues focused on myeloproliferative neoplasms (MPNs), a rare type of blood cancer involving the aberrant overproduction of blood cells. The majority of MPNs are linked to a specific mutation in the gene JAK2. When the mutation occurs in bone marrow stem cells, the body's blood cell production factories, it can erroneously activate JAK2 and trigger overproduction.

To pinpoint the origins of an individual's cancer, the team collected bone marrow stem cells from two patients with MPN driven by the JAK2 mutation. The researchers isolated a number of stem cells that contained the mutation, as well normal stem cells, from each patient, and then sequenced the entire genome of each individual cell.

Over time and by chance, the genomes of cells randomly acquire so-called somatic mutations--nonheritable, spontaneous changes that are largely harmless. Two cells that recently divided from the same mother cell will have very similar somatic mutation fingerprints. But two distantly related cells that shared a common ancestor many generations ago will have fewer mutations in common because they had the time to accumulate mutations separately.

Cell of origin

Analyzing these fingerprints, Hormoz and colleagues created a phylogenetic tree, which maps the relationships and common ancestors between cells, for the patients' stem cells--a process similar to studies of the relationships between chimpanzees and humans, for example.

"We can reconstruct the evolutionary history of these cancer cells,

going back to that cell of origin, the common ancestor in which the first mutation occurred," Hormoz said.

Combined with calculations of the rate at which mutations accumulate, the team could estimate when the JAK2 mutation first occurred. In the patient who was first diagnosed with MPN at age 63, the team found that the mutation arose around 44 years prior, at the age of 19. In the patient diagnosed at age 34, it arose at age 9.

By looking at the relationships between cells, the researchers could also estimate the number of cells that carried the mutation over time, allowing them to reconstruct the history of disease progression.

"Initially, there's one cell that has the mutation. And for the next 10 years there's only something like 100 cancer cells," Hormoz said. "But over time, the number grows exponentially and becomes thousands and thousands. We've had the notion that cancer takes a very long time to become an overt disease, but no one has shown this so explicitly until now."

The team found that the JAK2 mutation conferred a certain fitness advantage that helped cancerous cells outcompete normal bone marrow stem cells over long periods of time. The magnitude of this selective advantage is one possible explanation for some individuals' faster disease progression, such as the patient who was diagnosed with MPN at age 34.

In additional experiments, the team carried out single-cell gene expression analyses in thousands of bone marrow stem cells from seven different MPN patients. These analyses revealed that the JAK2 mutation can push stem cells to preferentially produce certain blood cell types, insights that may help scientists better understand the differences between various MPN types.

Together, the results of the study offer insights that could motivate new diagnostics, such as technologies to identify the presence of rare cancer-causing mutations currently difficult to detect, according to the authors.

"To me, the most exciting thing is thinking about at what point can we detect these cancers," Hormoz said. "If patients are walking into the clinic 40 years after their mutation first developed, could we have caught it earlier? And could we prevent the development of cancer before a patient ever knows they have it, which would be the ultimate dream?"

The researchers are now further refining their approach to studying the history of cancers, with the aim of helping clinical decision-making in the future.

While their approach is generalizable to other types of cancer, Hormoz notes that MPN is driven by a single mutation in a very slow growing type of stem cell. Other cancers may be driven by multiple mutations, or in faster-growing cell types, and further studies are needed to better understand the differences in evolutionary history between cancers.

The team's current efforts include developing early detection technologies, reconstructing the histories of greater numbers of cancer cells, and investigating why some patients' mutations never progress into full-blown cancer, but others do.

"Even if we can detect cancer-causing mutations early, the challenge is to predict which patients are at risk of developing the disease, and which are not," Hormoz said. "Looking into the past can tell us something about the future, and I think historical analyses such as the ones we conducted can give us new insights into how we could be diagnosing and intervening."

Study collaborators include scientists and physicians from Brigham and Women's Hospital, Boston Children's Hospital, Massachusetts General Hospital, and the European Bioinformatics Institute. The other co-corresponding authors of the study are Ann Mullally and Isidro Cortés-Ciriano.

Additional authors include Debra Van Egeren, Javier Escabi, Maximilian Nguyen, Shichen Liu, Christopher Reilly, Sachin Patel, Baransel Kamaz, Maria Kalyva, Daniel DeAngelo, Ilene Galinsky, Martha Wadleigh, Eric Winer, Marlise Luskin, Richard Stone, Jacqueline Garcia, Gabriela Hobbs, Fernando Camargo, and Franziska Michor.

The study was supported in part by the National Institutes of Health (grants

R00GM118910, R01HL158269), the Jayne Koskinas Ted Giovanis Foundation for Health and Policy, the William F. Milton Fund at Harvard University, an AACR-MPM Oncology Charitable Foundation Transformative Cancer Research grant, Gabrielle's Angel Foundation for Cancer Research, and the Claudia Adams Barr Program in Cancer Research. DOI: 10.1016/j.stem.2021.02.001

http://wb.md/3qlkeEx

Time to Rethink Prognosis After Prolonged Unconsciousness?

Most patients who become comatose after experiencing moderate or severe traumatic brain injury (TBI) recover consciousness in the short term — and nearly half regain functional independence, new research suggests.

Megan Brooks

The study, which included more than 17,000 patients who were hospitalized with moderate and severe TBI over three decades, showed that even when they remained unconscious at the end of their initial acute hospital care and were admitted for subsequent inpatient rehabilitation, 82% recovered consciousness by rehab completion.

"The results of our study, we think, show that caution is warranted in making decisions to withdraw or hold care in patients with these serious brain injuries," lead author Robert G. Kowalski, MBBCh, Department of Neurology, University of Colorado School of Medicine, Aurora, told *Medscape Medical News.*

"A meaningful recovery is possible, even when loss of consciousness occurs after the brain injury," he added.

The findings were published online March 1 in *JAMA Neurology*.

Self-fulfilling Prophecy?

TBI sends 2.9 million people to US emergency departments annually. More than half of patients with moderate to severe TBI become unconscious after the initial impact to the brain; and in many cases, this unconsciousness is deep (defined as coma) and persists for many hours, days, or weeks, Kowalski reported.

Historically, the prognosis of recovery for patients who have prolonged unconsciousness or disorders of consciousness (DOC) "has been perceived to be poor, with little hope for a return to independence," he said.

Therefore, in a significant proportion of cases, decisions are made to withdraw or withhold life-sustaining therapies, and the patients subsequently die. "This in turn contributes to the perception of poor prognosis in severe TBI — a so-called 'self-fulfilling prophecy,' " Kowalski noted.

The investigators evaluated the trajectory of, and factors associated with, recovery of consciousness and functional ability in patients with a DOC after moderate to severe TBI, focusing on the acute stage of emergent and critical care and subsequent inpatient rehabilitation.

"We chose this period of care, including the initial hospitalization and subsequent inpatient rehabilitation, because this is the time window during which treating medical teams and families make critical decisions that may prolong life and affect longer-term outcome for these patients, and help determine how successfully they are able to return to independent living," Kowalski said.

The cohort included 17,470 patients with moderate and severe TBI (median age at injury 39 years; 74% men). Of these, 7547 participants (57%) experienced initial loss of consciousness. This "loss of consciousness" state persisted to time of admission to acute rehabilitation (median days post-TBI, 25) in 2058 patients (12%).

However, 1674 comatose patients (82%) recovered consciousness (ability to follow commands) by the end of inpatient rehabilitation (median rehabilitation stay, 33 days). In addition, their trajectory of functional improvement mirrored that of patients with TBI who did not lose consciousness.

The investigators also observed the absence of specific signs of neuroanatomic injury on brain imaging, typically brain CT in the

acute phase of treatment, including blood in the ventricles of the brain and severe midline shift of cerebral structures. This absence portends better prospects for recovery of consciousness and functional ability for these patients, the researchers note.

"These findings may provide specific imaging thresholds upon which decisions can be made, using tools available to treating teams of TBI in most cases," Kowalski said.

"We think the results support the value of pursuing inpatient rehabilitation after initial hospital care for these patients, both in terms of recovery of consciousness and to aid a return to independence in daily life," he added.

Overly Nihilistic

In an accompanying editorial, Jennifer Kim, MD, PhD, and Kevin Sheth, MD, Division of Neurocritical Care, Yale School of Medicine, New Haven, Connecticut, note that the study "further challenges our potential toward overly nihilistic notions of who may, or may not, ultimately recover consciousness long term" by showing that a large proportion of patients with persistent DOC recover during acute rehabilitation.

"Other studies that followed up patients long term (not restricted to the inpatient rehabilitation period) corroborate the observation that recovery in TBI can occur 6 to 12 months after injury," they write.

The current study used one of the largest cohorts of patients with TBI available to assess recovery in the rehabilitation setting, and the "remarkable rate of recovery should give pause to practitioners who counsel families about potential recovery of DoC," write Kim and Sheth. "If there are no concerning radiographic features, then practitioners should communicate the potential for delayed DoC recovery," they add.

Echoing the investigators, the editorialists write that this study "adds to the TBI literature cautioning against withdrawal of life-sustaining therapy even when faced with prolonged DoC during hospitalization because there remains significant potential for recovery."

"Defining both good and poor prognostic risk factors is critical to portending recovery. Future work must refine biomarker identification and use in patients with DoC to improve physician prognostication and avoid self-fulfilling prophecy," they conclude.

The study had no commercial funding. Kowalski reported receiving grants from the National Institute on Disability, Independent Living, and Rehabilitation Research during the conduct of the study. Sheth reported receiving grants from the National Institutes of Health (NIH), the American Heart Association, Bard, Hyperfine, Biogen, and Novartis; other support from Zoll DSMB Chair and Alva Equity; and personal fees from NControl outside the submitted work. Kim reported receiving grants from the NIH, American Academy of Neurology, and Swebilius Foundation.

JAMA Neurol. Published March 1, 2021. Abstract, Editorial

http://bit.ly/3sQMRuQ

Smoking cessation drug may treat Parkinson's in women

Texas A&M researchers have found that that cytisine can reduce dopamine neuron loss, providing a protective effect against the neurodegenerative disorder.

Texas A&M University College of Medicine ressearchers have recently discovered that cytisine -- a smoking cessation drug commonly used in Europe -- reduces the loss of dopamine neurons in females. These findings provide potential evidence for the use of the drug to treat Parkinson's disease or stop its progression in women.

Sara Zarate and Gauri Pandey, graduate students from the lab of Rahul Srinivasan, assistant professor in the Department of Neuroscience & Experimental Therapeutics, are co-first authors of the research. Their findings are published in the *Journal of Neurochemistry*.

There are approximately 10 million people worldwide living with Parkinson's disease, a neurodegenerative disorder that leads to a variety of symptoms that can include difficulty walking, tremors,

shaking and others unrelated to movement. These symptoms start to develop when at least 50 percent of dopamine neurons in an individual's brain are dead or impaired. Currently, there is no cure for Parkinson's and no treatment that can stop or prevent the loss of these dopamine neurons that are needed for the body to move.

About a decade ago, Srinivasan became interested in trying to understand why smokers and people who consume tobacco chronically are at a lower risk for developing Parkinson's disease.

"Based on epidemiological studies, this phenomenon has been known for about 60 years," Srinivasan said. "But people really don't understand why that is, because tobacco and smoke contain so many different chemicals. One of the chemicals obviously is nicotine, and that explains the addictive properties of tobacco and cigarette smoke. So, I started to study the potential role of nicotine in this protective effect against Parkinson's disease."

Given the fact that it is very difficult to conduct human and animal trials using nicotine due to severe side-effects, Srinivasan decided to test cytisine as an alternative to nicotine. Cytisine is a smoking cessation drug with properties similar to nicotine, but with very few side effects in people.

"What cytisine does is it binds to target receptors but doesn't activate them as efficiently as nicotine," Srinivasan said. "It keeps the receptors 'occupied' and 'chaperones' them to the surface of the neuron. Since cytisine is a natural compound, is available quite freely and is pretty cheap, I decided to test this concept of chaperoning in an animal model of the disease to see if it works."

During experiments, the team artificially induced Parkinson's disease in animal models. During that time, they either gave them saline (salt water) or cytisine. Then, the researchers performed a series of behavioral experiments in order to see if there was any sort of protective effect on the animal models that were given cytisine.

Their findings showed that there was a protective effect both in terms of reducing the Parkinsonian behaviors and also in terms of reducing the number of dopamine neurons lost. However, the protective effect of cytisine occurred only in female animal models, and not in the males. They discovered that the combination of cytisine and estrogen produces a stronger protective effect than cytisine and no estrogen. This explains why the effect only occurred in female animal models, since males do not have appreciable amounts of estrogen.

Although their findings currently only apply to females, Srinivasan hopes to find solutions for males and postmenopausal females, too.

"What is really interesting is that there are non-feminizing compounds that have been developed and are being researched right now that can activate the receptors that estrogen activates," Srinivasan said. "The goal right now is to understand how estrogen triggers the protection in female animal models. Once we fully understand this component, then we can bring in these non-feminizing estrogen analogs, and we will potentially have a combination therapy of cytisine and a non-feminizing estrogen analog for men."

The next step for Srinivasan and his team is to solidify and confirm the role of estrogen specifically as a protective effect against Parkinson's disease. "At the face of it, this drug is ready to be used today in women with Parkinson's, but as is true for all drugs, you cannot get approval for a drug until you understand what the mechanism of the actual drug is exactly, which is our next step," Srinivasan said. "This first paper is the description of a protective effect and a potential mechanism for cytisine against Parkinson's disease. The next steps are to nail down the mechanisms by which this is happening, the role of estrogen specifically. Once we do that, we will use cytisine for women before menopause or cytisine combined with non-feminizing estrogen analogs for both men and women, including women after menopause."

http://bit.ly/3bpCsRq

Mysterious odor caused by BB pellet stuck in teen's nose for 8 years

When the teen blew his nose, a "pungent, foul odor filled the room," doctors said.

By Rachael Rettner - Senior Writer

A teen who had experienced years of nasal congestion along with a mysterious "foul odor" when he blew his nose turned out to have a BB gun pellet lodged in his nose, which had been there for about eight years, according to a new report.

The teen first visited doctors for his symptoms when he was 15 years old. He said he had experienced congestion for several years along with a reduced sense of smell, according to the report, published Feb. 18 in the journal JAMA Otolaryngology–Head & Neck Surgery.

Doctors examined the inside of the teen's nose with an endoscope, or a flexible tube with a camera at the end; and saw that he had so-called "turbinate hypertrophy," or an enlargement of narrow passageways called turbinates in the nose. This condition can sometimes be caused by seasonal allergies or sinus inflammation, according to Healthline.

Doctors prescribed the teen a nasal spray and antihistamine medication, and told him to come back in four to six weeks.

But the teen did not return until one year later, when he was 16, and he was still experiencing nasal symptoms. But now, when he blew his nose, "a pungent, foul odor filled the room," the authors said. "The patient reported that he did not feel he had bad breath, but he was embarrassed that every time he blew his nose there was a foul odor," they wrote.

Doctors then performed a CT scan and saw there was 9-mm spherical structure in his nasal cavity, which looked like a foreign body. The teen underwent surgery to remove the object, which turned out to be a metallic BB pellet.

A talk with the teen's family revealed that he had been shot in the nose with a pellet gun when he was about 8 or 9 years old, the report said. At the time, the boy hadn't experienced symptoms, and so his parents had not sought medical care.

Foreign objects lodged in the nose can sometimes cause a foul odor because "the foreign body causes blockage of natural drainage pathways in the nose, so there is a buildup of mucus, inhaled debris and bacteria," study co-author Dylan Z. Erwin, a medical student at The University of Texas Health Science Center at San Antonio, told Live Science. But this buildup doesn't always trigger a fever or other signs of a whole-body infection, and so the diagnosis can be missed, Erwin said.

In addition, the pellet in the boy's case was even harder to spot because over time, it had become covered with new tissue. "Healthy-appearing tissue had completely grown over it," Erwin said. For doctors to even see the pellet, this surrounding tissue had to be surgically removed, he said.

"It had become lodged in the floor of the nose beneath a structure called the inferior turbinate. It was essentially so tightly wedged, that blowing the nose didn't remove it and it was too far back to be easily seen," Erwin added.

Pellet gun injuries are common in adolescents, but the current case was unique because the injury happened so long ago, and the boy did not have symptoms of nasal trauma, the report said.

When a foreign body is stuck in the nose for a long period of time, doctors worry about a number of complications, including the development of an infection that spreads to the jaw or eyes; or the breakdown of nearby bone due to years of inflammation, Erwin said. In addition, there's also a risk that the patient could inhale the object if it became dislodged from the nose and goes down the back of the throat, he said.

Fortunately, the teen hadn't experienced any of these complications. After his surgery, his nose tissue appeared normal, and the unpleasant odor disappeared, the report said.

http://bit.ly/3bnXOyr

Humans evolved to be the water-saving ape

New study suggests humans evolved to run on less water than our closest primate relatives.

Durham, N.C. -- When you think about what separates humans from chimpanzees and other apes, you might think of our big brains, or the fact that we get around on two legs rather than four. But we have another distinguishing feature: water efficiency.

That's the take-home of a new study that, for the first time, measures precisely how much water humans lose and replace each day compared with our closest living animal relatives.

Our bodies are constantly losing water: when we sweat, go to the bathroom, even when we breathe. That water needs to be replenished to keep blood volume and other body fluids within normal ranges.

And yet, research published March 5 in the journal *Current Biology* shows that the human body uses 30% to 50% less water per day than our closest animal cousins. In other words, among primates, humans evolved to be the low-flow model.

An ancient shift in our body's ability to conserve water may have enabled our hunter-gatherer ancestors to venture farther from streams and watering holes in search of food, said lead author Herman Pontzer, associate professor of evolutionary anthropology at Duke University.

"Even just being able to go a little bit longer without water would have been a big advantage as early humans started making a living in dry, savannah landscapes," Pontzer said.

The study compared the water turnover of 309 people with a range of lifestyles, from farmers and hunter-gatherers to office workers, with that of 72 apes living in zoos and sanctuaries.

To maintain fluid balance within a healthy range, the body of a human or any other animal is a bit like a bathtub: "water coming in has to equal water coming out," Pontzer said.

Lose water by sweating, for example, and the body's thirst signals kick in, telling us to drink. Chug more water than your body needs, and the kidneys get rid of the extra fluid.

For each individual in the study, the researchers calculated water intake via food and drink on the one hand, and water lost via sweat, urine and the GI tract, on the other hand.

When they added up all the inputs and outputs, they found that the average person processes some three liters, or 12 cups, of water each day. A chimpanzee or gorilla living in a zoo goes through twice that much.

Pontzer says the researchers were surprised by the results because, among primates, humans have an amazing ability to sweat. Per square inch of skin, "humans have 10 times as many sweat glands as chimpanzees do," Pontzer said. That makes it possible for a person to sweat more than half a gallon during an hour-long workout -- equivalent to two Big Gulps from a 7-Eleven.

Add to that the fact that the great apes -- chimpanzees, bonobos, gorillas and orangutans -- live lazy lives. "Most apes spend 10 to 12 hours a day resting or feeding, and then they sleep for 10 hours. They really only move a couple hours a day," Pontzer said.

But the researchers controlled for differences in climate, body size, and factors like activity level and calories burned per day. So they concluded the water-savings for humans were real, and not just a function of where individuals lived or how physically active they were.

The findings suggest that something changed over the course of human evolution that reduced the amount of water our body uses each day to stay healthy.

Then as now, we could likely still only survive a few days without drinking, Pontzer said. "You probably don't break that ecological leash, but at least you get a longer one if you can go longer without water." The next step, Pontzer says, is to pinpoint how this physiological change happened.

One hypothesis, suggested by the data, is that our body's thirst response was re-tuned so that, overall, we crave less water per calorie compared with our ape relatives. Even as babies, long before our first solid food, the water-to-calories ratio of human breast milk is 25% less than the milks of other great apes.

Another possibility lies in front of our face: Fossil evidence suggests that, about 1.6 million years ago, with the inception of Homo erectus, humans started developing a more prominent nose. Our cousins gorillas and chimpanzees have much flatter noses.

Our nasal passages help conserve water by cooling and condensing the water vapor from exhaled air, turning it back into liquid on the inside of our nose where it can be reabsorbed.

Having a nose that sticks out more may have helped early humans retain more moisture with each breath.

"There's still a mystery to solve, but clearly humans are saving water," Pontzer said. "Figuring out exactly how we do that is where we go next, and that's going to be really fun."

This research was supported by the U.S. National Science Foundation (BCS-0643122, BCS-1317170, BCS-1440867, BCS-1440841, BCS-1440671), the United States Agency for International Development (APS-497-11-000001), the National Institutes of Health (R01DK080763), the John Templeton Foundation, L.S.B. Leakey Foundation, Wenner-Gren Foundation (Gr. 8670), the University of Arizona, Duke University, and Hunter College.

CITATION: "Evolution of Water Conservation in Humans," Herman Pontzer, Mary H. Brown, Brian M. Wood, David A. Raichlen, Audax. Z.P. Mabulla, Jacob A. Harris, Holly Dunsworth, Brian Hare, Kara Walker, Amy Luke, Lara R. Dugas, Dale Schoeller, Jacob Plange-Rhule, Pascal Bovet, Terrence E. Forrester, Melissa Emery Thompson, Robert W. Shumaker, Jessica M. Rothman, Erin Vogel, Fransiska Sulistyo, Shauhin Alavi, Didik Prasetyo, Samuel S. Urlacher, and Stephen R. Ross. Current Biology, March 5, 2021. DOI: 10.1016/j.cub.2021.02.045

http://bit.ly/3bpX0Zy

100-Million-Year-Old Seafloor Sediment Bacteria Have Been Resuscitated

The evidence mounts that bacteria can be effectively immortal

By Jennifer Frazer

In 2010, Japanese scientists from the Integrated Ocean Drilling Program's Expedition 329 sailed into the South Pacific Gyre with a giant drill and a big question.

The gyre is a marine desert more barren than all but the aridest places on Earth. Ocean currents swirl around it, but within the gyre, the water stills and life struggles because few nutrients enter. Near the center is both the Oceanic Pole of Inaccessibility (made famous by H.P. Lovecraft as the home of the be-tentacled Cthulhu) and the South Pacific garbage patch. At times the closest people are astronauts passing above on the International Space Station.

The sea here is so miserly that it takes one million years for a meter of marine "snow"—corpses, poo and dust—to accumulate on the bottom. The tale of all that time can total as little as 10 centimeters. It is the least productive patch of water on the planet.

Through nearly 6,000 meters of this seawater the IODP team lowered a drill. The strawlike bit plunged into pelagic clay and calcareous nanofossil ooze at three sites on the bottom.

By the time the cores of sediment were raised to the surface, the tubes contained up to 100 million years of Earth history. What the team wanted to know was how long and in what state microbes trapped in this milieu could survive in an almost-completely raided oceanic refrigerator. They were in for a surprise.

Their results, published in *Nature Communications* in July, revealed that the sediments contained bacterial cells, which they expected (not many, though: just 100 to 3,000 per cubic centimeter). But when given food, most of them quickly revived, which the scientists did not expect.

The microbes got straight to work doing what bacteria do, and within 68 days of incubation had increased their numbers up to 10,000-fold. They doubled about every five days (*E. coli* bacteria in the lab double in around 20 minutes). Their progeny contained specially labeled isotopes of carbon and nitrogen that made the scientists sure that the microbes were eating what they had been offered.

It's worth pausing to consider the meaning of these results. In this experiment, cells awoke and multiplied that settled to the bottom when pterosaurs and plesiosaurs drifted overhead. Four geologic periods had ground by, but these microbes, protected from radiation and cosmic rays by a thick coat of ocean and sediment, quietly persisted. And now, when offered a bite, they awoke and carried on as if nothing unusual had happened.

In a sense, it hadn't. If you think it feels like 100 million years since the pandemic began, think about the conditions (and entertainment options) of these poor microbes. It was a *really* long 100 million years down there. The toll of all that time was not zero, though. The oldest cells multiplied about half as fast as their spryer brethren that had "only" been there a few million years.

Consider now that 70 percent of Earth's surface is covered by marine sediment, whose microbial residents represent somewhere between a tenth and a half of all microbial biomass on Earth. There's a whole lot of senior citizen microbes down there.

Somewhat surprisingly, the majority of the cells were, like us, forms that breathe oxygen. In fact, the sediment they were pulled from is full of oxygen. Clearly, lack of "air" is not the problem for the life in gyre sediments. It's the lack of food.

Contributing to the problem is the density of the sediment, which approaches something like flourless chocolate cake: the pore size is an estimated 0.02 micrometers. Given that a typical bacterium is a few micrometers across, you can see the problems inherent to migrating in search of food, or even hoping some blunders into you. Once you end up in South Pacific Gyre seafloor sediment, you are trapped—unless rescued by an ocean drilling program.

More surprises lay in store when the scientists checked the identities of the cells by probing their DNA; there was a lack of spore-forming bacteria. Some bacteria make resistant structures called endospores that are fortified and metabolically inactive, seemingly formed to allow bacteria to endure harsh conditions. Yet these bacteria were relatively absent. Spores were *not* how these superannuated bacteria had survived.

Even more surprising, discovered in one sample was a thriving population of light-harvesting bacteria called *Chroococcidiopsis*, cyanobacteria with a reputation for survival so formidable that they are being considered for terraforming Mars. (In addition to being able to live under translucent rocks in dry, cold, salty and radiation-drenched places, they have the unusual ability to capitalize on red light, possibly a result of their preferred dim conditions). How these photosynthetic microbes managed to reproduce in the dark after 13 million years beneath the seafloor remains a mystery.

Putting it all together—the tight quarters, the lack of spores and the rapid reanimation—these scientists think it's likely that the majority of the bacteria in this impoverished sediment have been alive but idling these 100 million years.

A few years ago, I wrote about bacteria that may have been resurrected from coal from the Paleozoic. Now we have reports of bacteria from the Cretaceous seafloor sediment waking apparently nonplussed. Back then I speculated that under certain highly constrained but possibly abundant conditions, bacteria may be effectively immortal. Now it seems even more likely we may be sitting atop a planet that's full of living fossils that are literally that—both fossils and alive.

The dinosaur people (and to be fair, who among us aren't dinosaur

people?) have their museums filled with bones and teeth and tracks. The plant people have their petrified forests and fossil fronds. But the microbe people have something even better: our dinosaurs aren't dead.

http://bit.ly/38ieGob

For The First Time, Organic Matter Crucial For Life Has Been Found on an Asteroid's Surface

First evidence of organic materials essential to life on the surface of an asteroid

Mike McRae

Follow the twisted limbs of your family tree all the way back to its primordial origins billions of years in the past and you'll find that we all originated from dust rich in organic chemistry.

Just where this organic dust came from has been a topic of debate for more than half a century. Now, researchers have found the first evidence of organic materials essential to life on Earth on the surface of an S-type asteroid.

An international team of researchers recently conducted an in-depth analysis on one of the particles brought back from the asteroid Itokawa by the Japanese Space Agency's (JAXA) original Hayabusa mission back in 2010.

Most of Earth's meteorites come from S-type asteroids like Itokawa, so knowing that it could have contained essential ingredients for life on our planet is a significant step forward in our understanding of how life-forming conditions could arise. Up until now, most research on organic material has focussed on carbon-rich (c-class) asteroids.

Looking into the sample, the team found that organic material that came from the asteroid itself has evolved over time through extreme conditions - incorporating water and organic matter from other sources. This is similar to the process that happened on Earth, and helps us better understand how the earliest forms of terrestrial biochemistry might simply be an extension of the chemistry taking place inside many asteroids.

"These findings are really exciting as they reveal complex details of an asteroid's history and how its evolution pathway is so similar to that of the prebiotic Earth," says earth scientist Queenie Chan from the Royal Holloway University of London.

Evolutionary models can take us back some 3.5 billion years to a time when life was little more than competing sequences of nucleic acid. Step back any further and we're forced to consider how elements like hydrogen, oxygen, nitrogen, and carbon might join to form amazingly complex molecules capable of self-arranging into stuff that behaves like RNA, proteins, and fatty acids.

In the 1950s, as researchers were first considering the prickly question of how simpler ingredients might spontaneously cook up an organic soup, experiments showed conditions on Earth's surface might do a sufficient job. Nearly seven decades later, our focus has turned to the slow and steady chemical processes inside the very rocks that aggregated into worlds like ours.

Evidence isn't hard to come by. It's now clear a steady rain of rock and ice billions of years ago could have delivered molecules of cyanide, the sugar ribose, and even amino acids – along with a generous donation of water – onto Earth's surface.

But the degree to which the chemistry of meteorites could have been contaminated by things on Earth leaves some room for doubt.

Since Hayabusa's return a decade ago, more than 900 particles of pristine asteroid dirt taken from its payload have been separated and stored in a JAXA clean room. Fewer than 10 have been studied for signs of organic chemistry, but all of them were found to contain molecules predominantly made up of carbon.

Itokawa is what's referred to as a stony (or siliceous) class of asteroid, or s-class. Following early studies on its material, it's also believed to be an ordinary chondrite – a relatively unmodified type

of space rock representing a more primitive state of the inner Solar System. Given these types of asteroids make up a good chunk of the minerals smashing into our planet, and aren't generally thought to contain much in the way of organic chemistry, those early findings were intriguing, to say the least.

Chan and her colleagues took just one of these grains of dust, a 30 micrometre wide particle shaped a little like the continent of South America, and conducted a detailed analysis of its make-up, including a study of its water contents.

They found a rich variety of carbonaceous compounds, including signs of disordered polyaromatic molecules of a clearly extraterrestrial origin, and structures of graphite.

"After being studied in great detail by an international team of researchers, our analysis of a single grain, nicknamed 'Amazon', has preserved both primitive (unheated) and processed (heated) organic matter within ten microns (a thousandth of a centimetre) of distance," says Chan.

"The organic matter that has been heated indicates that the asteroid had been heated to over 600°C in the past. The presence of unheated organic matter very close to it, means that the in-fall of primitive organics arrived on the surface of Itokawa after the asteroid had cooled down."

Itokawa has had an exciting history for a rock that has nothing better to do than float idly around the Sun for a few billion years, having been modified with a good baking, dehydrated, then rehydrated with a new coating of fresh material. While its story isn't quite as exciting as our own planet's history, the asteroid's activity does describe the cooking of organic material in space as a complex process, and isn't limited to carbon-rich asteroids.

Late last year, Hayabusa2 returned with a sample of a c-class, near-Earth asteroid named Ryugu. Comparing the contents of its payload with those of its predecessor will no doubt contribute even more knowledge of how organic chemistry evolves in space.

The question of life's origins and its seeming uniqueness on Earth is one that we'll be seeking answers to for a long time to come. But every new discovery is pointing to a story that stretches far beyond the safe, warm puddles our newborn planet.

This research was published in *Scientific Reports*.

http://bit.ly/38hwDTH

New test enables rapid detection of mild cognitive impairment as well as dementia

Researchers from Kanazawa University develop a new efficient way to screen for mild cognitive impairment and dementia

Kanazawa, Japan - As the global population ages, the rate of dementia is increasing worldwide. Given that early detection is critical for treatment, effective ways to screen for dementia are a high research priority. Now, researchers from Japan have developed a new screening tool that can be administered in a matter of minutes.

In a study published in *PLOS ONE*, researchers from Kanazawa University have revealed a new computerized cognitive test, termed the computerized assessment battery for cognition (C-ABC), which they found to be effective in screening for both dementia and mild cognitive impairment (MCI) in just 5 minutes.

The computerized assessment battery for cognition (C-ABC). The figures-recognition memory test is shown: "please touch the figures with same color and shape as those presented before." **Kanazawa University**

Computerized cognitive tests are frequently chosen over paper-and-pencil versions because they are more precise and do not require training to administer. However, computerized cognitive tests for dementia and MCI generally take 10-30 minutes to complete. Further, the wide range of existing tests can make it difficult for

healthcare practitioners to choose one that is suitable for detecting dementia or MCI. The researchers at Kanazawa University aimed to address this by creating a test that could be used to accurately and efficiently screen for both conditions.

"Although patients with dementia usually have disorientation and severe memory disturbance, those with MCI and those with normal cognition rarely have both," says co-lead author of the study Moeko Noguchi-Shinohara. "We wanted to develop a test that could distinguish these cognitive states in an efficient manner."

To do this, the researchers collected C-ABC scores from participants in different age groups (50s, 60s, and those aged 70-85 years) with dementia, MCI, and normal cognition. They then conducted a range of statistical tests to determine whether the test could distinguish normal cognition, dementia, and MCI.

"The results were surprising," explains Masahito Yamada, senior author. "We found that the C-ABC could distinguish individuals with MCI from those with normal cognition using scores from items that only took 5 minutes to complete."

In fact, in the 75-80 age group, answers from just two questions could distinguish participants with MCI from those with normal cognition, and these two items took just 2 minutes to complete.

"When we compared our C-ABS scores with those from the frequently used Mini-Mental State Examination (MMSE), we found a high correlation. However, the C-ABC is substantially faster to complete than the MMSE, and may be more sensitive to MCI or mild dementia," says Yamada.

The data indicate that when used with a high cut-off score for sensitivity, the C-ABC is appropriate for initial screening for dementia and MCI. This new tool could make cognitive screening more accessible and efficient, thus enabling earlier detection of MCI or dementia. This, in turn, could improve the treatment options and overall outcome for individuals with MCI or dementia.

http://wb.md/3sT3UMQ

Cancer Drugmaker Destroyed Records Before FDA Inspection

$50 Million in Fines and Forfeiture

Pleaded guilty to concealing and destroying records prior to an inspection by the Food and Drug Administration

Nick Mulcahy

A company that manufacturer ingredients for cancer drugs used in the United States has pleaded guilty to concealing and destroying records prior to an inspection by the Food and Drug Administration (FDA) and will pay $50 million in fines and forfeiture.

The company, Fresenius Kabi Oncology Limited, has also agreed to implement a compliance and ethics program to adhere to US standards.

Fresenius Kabi owns and operates a plant in Kalyani, West Bengal, India, that manufactured active pharmaceutical ingredients used in "various cancer products" distributed to the US, according to a Department of Justice (DOJ) statement.

The FDA conducted a plant inspection at the factory in India in 2013. The company removed and destroyed records that "would have revealed [that it] was manufacturing ingredients in contravention of FDA requirements," the DOJ said.

Fresenius Kabi Oncology Limited was charged with violating the Federal Food, Drug, and Cosmetic Act by failing to provide required records to FDA investigators. The company is guilty of a misdemeanor. As noted above, it will pay $50 million to the US government, which comprises a $30 million fine and $20 million forfeiture.

"Fresenius Kabi Oncology Limited's conduct put vulnerable patients at risk. The Department of Justice will continue to work with FDA to prosecute drug manufacturers who obstruct these inspections," said Acting Assistant Attorney General Brian Boynton

of the DOJ's Civil Division.

Company Responds

The employees who failed to provide the FDA with the required information were terminated in 2013, according to a statement sent to *Medscape Medical News* from the parent corporation, Fresenius Kabi in Bod Homburg, Germany.

"We continuously strive for the highest standards in pharmaceutical manufacturing," said Mats Henriksson, company CEO.

The US agency did not specify which ingredients or what cancer drugs were affected in its statement.

The company website says that its oncology products include ingredients for injectables (liquid, dry, lyophilized), tablets, and capsules.

Case documents were made public in February, but were not yet accessible when this story went to press. The documents include the criminal indictment, which contains the comprehensive details of the case.

"We are working with the court to get the documents online as the case is now unsealed," said Nicholas Dickinson, assistant US attorney in Nevada, in a February email to *Medscape Medical News*.

http://bit.ly/3efj9fb

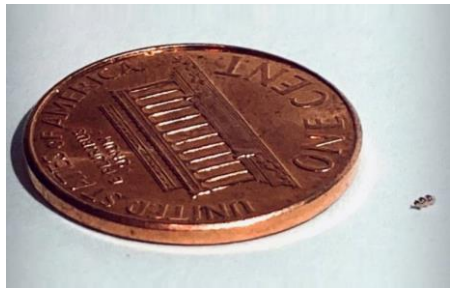
The answer to cancer might be these tiny robots

Drug delivery robots may ultimately help eliminate tumors by directing them within your body

By Mike Wehner

Cancer treatments have improved dramatically over the past few decades. Many types of cancer have a high survival rate thanks to medical interventions that can slow or stop the growth of tumors and even eliminate them entirely. Despite that, cancer remains the second leading cause of death in the United States, right behind heart disease, and there's still no go-to cure that is applicable to all or even the majority of cancer cases. It would be great if that changed, and a startup in California thinks that tiny robots might be the answer.

The company is Bionaut Labs, and as the *Los Angeles Times* reports, the team has been toiling in the hopes of perfecting a robot-powered drug delivery system that is so tiny it looks like a speck of dirt to the naked eye. Yes, drug-carrying robots may ultimately help eliminate tumors by "driving" to them inside of your body.



A tiny Bionaut device sitting next to a penny. **Image source: Bionaut Labs**

The idea sounds like something out of a science fiction story — and there are several such movies and books that make use of miniaturized robots inside the human body for good and ill — but this is the real deal. Bionaut Labs wants to do away with the imprecise nature of most therapeutic cancer treatments, and its screw-shaped robots could do just that.

It's an incredibly simple concept: Bionaut's tiny bots are small enough to be injected into a human body without much discomfort and, once inside, their screw-like shape allows them to be directed to the offending tumor using external magnets that produce a magnetic field. All the while, doctors monitor the progress of the bots on a live X-ray feed, ensuring they're heading in the right direction and bringing straight to the cancerous growth.

Once the bot (or, in most cases, multiple bots) make it to the destination, a command is sent to the devices also using magnets. This prompts the devices to dump their drug payload right on the tumor itself, maximizing its effectiveness while hopefully minimizing any side effects.

Compare this to a therapeutic approach involving drugs that are swallowed or even injected and you can see the benefit. Getting a cancer-fighting drug to a tumor is normally something that has to

be done by the circulatory system, and that means spreading the chemical throughout the entire body. It works, but it can also produce side effects and it's not nearly as efficient as it could be if tiny robots were delivering the drugs.

I think what's most interesting about this new report is that this isn't some pie-in-the-sky dream scenario. This is actually a real technology that is already being proven in the real world. The company is targeting specific types of cancers that affect the brain stem right now, injecting the bots into the spinal column where they can travel to the site of the cancer, but as the technology advances, it could become just as effective against other cancer variants.

Based on the company's roadmap, clinical trials could happen as early as 2023, paving the way for regulatory approval which would add it to the arsenal of cancer treatment options for specialists around the world.