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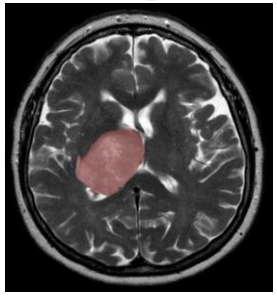
Brain cancer linked to tissue healing

Brain tumours might arise when tissue does not heal properly-- a finding that opens up new ideas about how cancer develops and how to combat it



The healing process that follows a brain injury could spur tumour growth when new cells generated to replace those lost to the injury are derailed by mutations, Toronto scientists have found. A brain injury can be anything from trauma to infection or stroke.

A brain scan showing a top down view of a cross-section with a glioblastoma tumour highlighted in red. **Hellerhoff, Wikimedia Commons**

The findings were made by an interdisciplinary team of researchers from the University of Toronto, The Hospital for Sick Children (SickKids) and the Princess Margaret Cancer Centre who are also on the pan-Canadian Stand Up To Cancer Canada Dream Team that focuses on a common brain cancer known as glioblastoma.

"Our data suggest that the right mutational change in particular cells in the brain could be modified by injury to give rise to a tumour," says Dr. Peter Dirks, Dream Team leader who is the Head of the Division of Neurosurgery and a Senior Scientist in the Developmental and Stem Cell Biology program at SickKids.

Gary Bader, a professor of molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research at U of T's Temerty Faculty of Medicine and Dr. Trevor Pugh, Senior Scientist at the Princess Margaret, also led the research which has been published today in the journal *Nature Cancer*.

The findings could lead to new therapy for glioblastoma patients who currently have limited treatment options with an average lifespan of 15 months after diagnosis. "Glioblastoma can be thought of as a wound that never stops healing," says Dirks. "We're excited about what this tells us about how cancer originates and grows and it opens up entirely new ideas about treatment by focusing on the injury and inflammation response."

The researchers applied the latest single-cell RNA sequencing and machine learning technologies to map the molecular make-up of the glioblastoma stem cells (GSCs), which Dirks' team previously showed are responsible for tumour initiation and recurrence after treatment.

They found new subpopulations of GSCs which bear the molecular hallmarks of inflammation and which are comingled with other cancer stem cells inside patients' tumours. It suggests that some glioblastomas start to form when the normal tissue healing process, which generates new cells to replace those lost to injury, gets derailed by mutations, possibly even many years before patients become symptomatic, Dirks said.

Once a mutant cell becomes engaged in wound healing, it cannot stop multiplying because the normal controls are broken and this spurs tumour growth, according to the study.

"The goal is to identify a drug that will kill the glioblastoma stem cells," says Bader, whose graduate student Owen Whitley contributed to the computational data analysis "But we first needed to understand the molecular nature of these cells in order to be able to target them more effectively."

The team collected GSCs from 26 patients' tumours and expanded them in the lab to obtain sufficient numbers of these rare cells for analysis. Almost 70,000 cells were analyzed by single-cell RNA sequencing which detects what genes are switched on in individual cells, an effort led by Laura Richards, a graduate student in Pugh's lab.

The data confirmed extensive disease heterogeneity, meaning that each tumour contains multiple subpopulations of molecularly

distinct cancer stem cells, making recurrence likely as existing therapy can't wipe out all the different subclones.

A closer look revealed that each tumour has either of the two distinct molecular states--termed "Developmental" and "Injury Response"-- or somewhere on a gradient between the two.

The developmental state is a hallmark of the glioblastoma stem cells and resembles that of the rapidly dividing stem cells in the growing brain before birth.

But the second state came as a surprise. The researchers termed it "Injury Response" because it showed an upregulation of immune pathways and inflammation markers, such as interferon and TNFalpha, which are indicative of wound healing processes.

These immune signatures were only picked up thanks to the new single-cell technology after being missed by older methods for bulk cell measurements.

Meanwhile, experiments led by Stephane Angers' lab at the Leslie Dan Faculty of Pharmacy established that the two states are vulnerable to different types of gene knock outs, revealing a swathe of therapeutic targets linked to inflammation that had not been previously considered for glioblastoma.

Finally, the relative comingling of the two states was found to be patient-specific, meaning that each tumour was biased either toward the developmental or the injury response end of the gradient. The researchers are now looking to target these biases for tailored therapies.

"We're now looking for drugs that are effective on different points of this gradient", says Pugh, who is also the Director of Genomics at the Ontario Institute for Cancer Research. "There's a real opportunity here for precision medicine-- to dissect patients' tumours at the single cell level and design a drug cocktail that can take out more than one cancer stem cell subclone at the same time."

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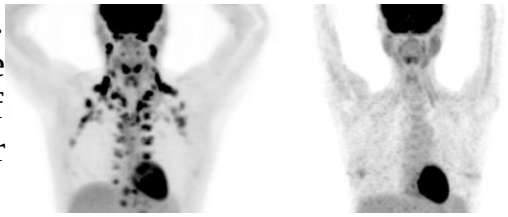
Study of Over 50,000 People Links Brown Fat With Better Health Outcomes

A large new study has provided strong evidence that people with brown fat in their bodies are less likely to suffer from a range of health conditions.

Jacinta Bowler

"For the first time, it reveals a link to lower risk of certain conditions," says one of the researchers, Rockefeller University Hospital physician Paul Cohen. "These findings make us more confident about the potential of targeting brown fat for therapeutic benefit."



PET scans showing someone with brown fat (l) and no brown fat. **(Andreas G. Wibmer/Heiko Schöder/MSKCC)**

Brown fat or brown adipose tissue (BAT) is particularly common in hibernating mammals and newborns. BAT helps mammals regulate temperature - when we're really cold, the large amounts of mitochondria found in this type of fat tissue burn energy and produce heat. In fact, the iron-rich mitochondria are what gives brown fat its characteristic colour.

It wasn't until 2009 that scientists discovered some adult humans have brown fat in their bodies as well, usually around the neck and shoulders.

There have been plenty of mouse studies looking at the benefit of having brown fat, but in humans the research has been murkier until recently. Having brown fat seems to improve a person's metabolism and may even help to lose weight (although the latter is probably not quite as simple). "The natural question that everybody has is, 'What can I do to get more brown fat?'" Cohen says.

"We don't have a good answer to that yet, but it will be an exciting space for scientists to explore in the upcoming years."

Looking at a large dataset of 52,487 participants undergoing PET/CT scans for cancer evaluation, the team found evidence of brown fat in just under 10 percent of cases (5,070 people).

The researchers think this might be an underestimation because of the conditions the participants were under - they were told to avoid cold exposure, exercise, and caffeine before the scans, all of which have been linked to brown fat activity.

Around 4.6 percent of those with brown fat also had type 2 diabetes, while that number was 9.5 percent in the 'no brown fat' group. A similar result was seen in abnormal cholesterol results – 18.9 percent of people with brown fat had abnormal cholesterol, compared to 22.2 percent of people who didn't have brown fat.

Hypertension, congestive heart failure, and coronary artery disease also saw small positive differences in the brown fat vs no brown fat groups.

"These findings were supported by improved blood glucose, triglyceride and high-density lipoprotein values," the team writes in their new paper.

While the numbers here are exciting, there's no evidence as yet that brown fat makes you immune to any of these conditions - but there's a link to reduced risk worth exploring further.

What was really interesting though is that brown fat was particularly protective in those that were obese. Those obese patients that had brown fat had similar prevalence of these metabolic and heart conditions as non-obese people.

"It almost seems like they are protected from the harmful effects of white fat," says Cohen.

"Taken together, our findings highlight a potential role for BAT in promoting cardiometabolic health," the researchers note in their paper.

It's important to note that the data the researchers were working with came from cancer evaluations at the Memorial Sloan Kettering Cancer Center, meaning this is not a sample representative of the general population.

Nevertheless, the study has yielded a fascinating new look at the role of brown fat in the human body, and will hopefully lead to even more discoveries in the future.

"We are considering the possibility that brown fat tissue does more than consume glucose and burn calories, and perhaps actually participates in hormonal signaling to other organs," says Cohen.

The research has been published in *Nature Medicine*.

http://bit.ly/2LBfLPe

Bedside EEG test can aid prognosis in unresponsive brain injury patients

Could yield important insights into how they might recover

Assessing the ability of unresponsive patients with severe brain injury to understand what is being said to them could yield important insights into how they might recover, according to new research.

A team at the University of Birmingham has shown that responses to speech can be measured using electroencephalography, a non-invasive technique used to record electrical signals in the brain. The strength of these responses can be used to provide an accurate prognosis that can help clinicians make the most effective treatment decisions.

Significantly the assessments can be made while the patient is still in intensive care and does not require any conscious response from the patient - they do not have to 'do' anything.

In the study, published in *Annals of Neurology*, the team assessed 28 patients with acute traumatic brain injury (TBI) who were not under sedation, and who failed to obey commands.

The patients were assessed within just a few days of their injury. They were played streams of sentences and phrases made up of monosyllabic words while their brain activity was monitored using EEG.

In healthy individuals, EEG activity only synchronises with the rhythm of phrases and sentence when listeners consciously comprehend the speech. The researchers assessed the level of the unresponsive patients' comprehension by measuring the strength of this synchronicity.

The researchers were able to follow up 17 of the patients three months following their injury, and 16 of the patients after six months. They found the outcomes significantly correlated with the strength of the patients' response to speech measured by the EEG.

Patients with traumatic brain injury are commonly assessed by their behaviour or by a CT scan, but some patients who remain unresponsive pose a significant challenge.

Recent studies have shown that TBI patients can be shown to 'imagine' themselves following commands. This activity can also be tracked using EEG. However, this approach requires a fairly sophisticated response from the patient, so patients with lower brain capabilities may be overlooked.

Lead author Dr Damian Cruse is based at the University of Birmingham's School of Psychology and Centre for Human Brain Health. He explains: "The strength of our approach is that we can measure a scale of comprehension without needing any other sort of response from the patient. This insight could significantly reduce prognostic uncertainty at a critical point. It could help clinicians make more appropriate decisions about whether or not to continue life-sustaining therapy - and also ensure rehabilitation resources are allocated to patients who are most likely to benefit."

Cruse et al (2020). 'Covert speech comprehension predicts recovery from acute post-traumatic unresponsive states.' Annals of Neurology.

http://bit.ly/3nxHpu8

COVID-19 vaccines may not work as well against South African variant, experts worry

A coronavirus variant identified in South Africa may not be as vulnerable to COVID-19 vaccines as other strains, some scientists say.

By Nicoletta Lanese - Staff Writer

Studies are now underway to find out if that's actually the case.

If the variant, known as 501.V2, is resistant to available vaccines, the shots could be tweaked to boost their effectiveness — adjustments that would take about six weeks to make, vaccine developers told Reuters. These developers included BioNTech CEO Dr. Uğur Şahin and John Bell, Regius Professor of Medicine at the University of Oxford, who are currently running experiments with both 501.V2 and the new coronavirus variant identified in the U.K., named B.1.1.7.

These experiments are so-called neutralizing assays — experiments in which they incubate the viruses with antibodies and human cells, to see if the antibodies prevent infection, The Associated Press (AP) reported. They are running the tests with blood from vaccinated people and those who caught the virus and developed antibodies naturally, Dr. Richard Lessells, an infectious diseases expert who is working on South Africa's genomic studies of 501.V2, told the AP.

In general, it's not surprising that variants like 501.V2 and B.1.1.7 have emerged; all viruses pick up mutations as they make copies of themselves, and the novel coronavirus called SARS-CoV-2 is no exception. However, while the two recently identified variants share a few similar mutations, and 501.V2 "has a number additional mutations ... which are concerning," Simon Clarke, an associate professor in cellular microbiology at the University of Reading, told Reuters.

Specifically, the variant found in South Africa has more mutations in its spike protein — which sticks out from the virus's surface and is used to invade human cells — than B.1.1.7 does, Lawrence Young, a virologist and professor of molecular oncology at Warwick University, told Reuters. Most available vaccines train the immune system to recognize this spike protein. If the spike protein accumulates too many mutations, it may become unrecognizable to the immune system, allowing the virus to avoid detection in the body; this is the potential concern with the new variant 501.V2, Young said.

That said, neutralizing assays should soon reveal whether or not we need to worry. As of now, Public Health England, an executive agency of the Department of Health and Social Care, said that there is currently no evidence to suggest COVID-19 vaccines won't protect against both B.1.1.7 and 501.V2, Reuters reported.

In addition, several experts told The New York Times that it would likely take years, not months, for the coronavirus to mutate enough to outwit available vaccines.

"It is going to be a process that occurs over the time scale of multiple years and requires the accumulation of multiple viral mutations," Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle, told the Times. "It's not going to be like an on-off switch," in terms of how quickly new variants become resistant to current vaccines, he said. In other words, vaccines might become gradually less effective over time, rather than suddenly not working.

http://bit.ly/2XpfEsN

An epidemic of overdiagnosis: Melanoma diagnoses sky rocket

Melanoma of the skin is now the third most commonly diagnosed cancer in the US

WHO H. Gilbert Welch MD, MPH, Senior Investigator, Center for Surgery and Public Health, Brigham and Women's Hospital; co-author of a new Sounding Board article published in The *New England Journal of Medicine*.

WHAT Melanoma of the skin is now the third most commonly diagnosed cancer in the U.S. Diagnoses of melanoma are six times as high today as they were 40 years ago. While incidence of melanoma has been rising steeply, melanoma mortality has been generally stable. In a Sounding Board article, Welch and colleagues present evidence for why they believe that increased diagnostic scrutiny is the primary driver of the rapid rise in melanoma diagnoses.

"Melanoma is now the posterchild for overdiagnosis," said Welch. "Although the conventional response has been to recommend regular skin checks, it is far more likely that more skin checks are the cause of the epidemic -- not its solution."

Among many examples, Welch and co-authors describe a study in which nine dermatopathologists reviewed skin-biopsy specimens used for diagnosis 20 years earlier. Many of the specimens previously diagnosed as benign were now diagnosed as melanoma. Welch and co-authors also share data showing that among the Medicare population, the proportion of beneficiaries biopsied increased every year from 2004 to 2017, nearly doubling over that time. Over the same period, the incidence of melanoma in adults 65 and older also doubled.

The authors point out that there are many potential harms in over-diagnosing melanoma, from the immediate -- scarring, wound infection, out-of-pocket costs -- to longer term effects such as impeding access to care for people with symptomatic skin diseases.

"Despite the best of intentions by all parties, increased diagnostic scrutiny can produce a cycle of increasing overdiagnosis and intervention in any disease with a reservoir of subclinical forms.

Melanoma is no exception," the authors write. "The economic disruption caused by Covid-19 obliges clinicians to protect people from the financial stress of needlessly being turned into a patient."

http://bit.ly/3noT7ak

Gut microbe may promote breast cancers

Short-term exposure to B. fragilis toxin leaves lasting impression in cells, increasing the risk for cancer

A microbe found in the colon and commonly associated with the development of colitis and colon cancer also may play a role in the development of some breast cancers, according to new research from investigators with the Johns Hopkins Kimmel Cancer Center and its Bloomberg~Kimmel Institute for Cancer Immunotherapy. Breast tissue cells exposed to this toxin retain a long-term memory, increasing the risk for disease.

In a series of laboratory experiments, researchers discovered that when enterotoxigenic Bacteroides fragilis (ETBF) was introduced to the guts or breast ducts of mice, it always induced growth and metastatic progression of tumor cells. A description of the work is published in the January 6 issue of the journal *Cancer Discovery*.

While microbes are known to be present in body sites such as the gastrointestinal tract, nasal passages and skin, breast tissue was considered sterile until recently, says senior study author Dipali Sharma, Ph.D., a professor of oncology at Johns Hopkins Medicine.

The study is a first step to show the involvement of ETBF in breast cancer development, Sharma says. Additional studies are needed to clarify how ETBF moves throughout the body, whether ETBF can be a sole driver to directly trigger the transformation of breast cells in humans, and/or if other microbiota also have cancer-causing activity for breast tissue.

"Despite multiple established risk factors for breast cancer, such as age, genetic changes, radiation therapy and family history, a large number of breast cancers arise in women harboring none of these, indicating the need to look beyond," Sharma says. "Our study suggests another risk factor, which is the microbiome. If your microbiome is perturbed, or if you harbor toxigenic microbes with oncogenic function, that could be considered an additional risk factor for breast cancer."

Sharma and colleagues performed several experiments to study the role of ETBF. First, they performed a meta-analysis of clinical data looking at published studies comparing microbial composition among benign and malignant breast tumors and nipple aspirate fluids of breast cancer survivors and healthy volunteers. B. fragilis was consistently detected in all breast tissue samples as well as the nipple fluids of cancer survivors.

In the lab, the team gave the ETBF bacteria by mouth to a group of mice. First, it colonized the gut. Then, within three weeks, the mouse mammary tissue had observable changes usually present in ductal hyperplasia, a precancerous condition. In additional tests, investigators found that hyperplasia-like symptoms also appeared within two to three weeks of injecting ETBF bacteria directly to the teats of mice, and that cells exposed to the toxin always exhibited more rapid tumor progression and developed more aggressive tumors than cells not exposed to the toxin. Breast cells exposed to the toxin for 72 hours retained a memory of the toxin and were able to start cancer development and form metastatic lesions in different mouse models. Investigators also found the Notch1 and beta-catenin cell signaling pathways to be involved in promoting EBFT's role in breast tissue.

In clinical studies, the investigators have started looking for microbiome changes among breast cancer patients to see how this impacts tumor progression and response to therapy. Meanwhile, Sharma says, "we definitely should try to maintain a healthy microbiome, including eating a healthy diet and exercising, and maintaining the correct body mass index."

Down the road, screening for microbiome changes could be as simple as stool sample tests, said lead author Sheetal Parida, a postdoctoral fellow at Johns Hopkins Medicine. "This is just one indicator, and we think there will be multiple," she said. "If we find additional bacteria responsible for cancer development, we can easily look at the stool and check for those. Women at high risk of developing breast cancer might have a high population of some of these."

The work was supported by the National Cancer Institute (grants R01CA204555 and CA183804), the Breast Cancer Research Foundation, and Bloomberg Philanthropies. Study co-authors were Shaoguang Wu, Sumit Siddarth, Guannan Wang, Nethaji Muniraj, Arumugam Nagalingam, Christina Hum, Panagiotis Mistriotis, Haiping Hao, C. Conover Talbot Jr., Konstantinos Konstantopoulos, Kathleen L. Gabrielson and Cynthia L. Sears.

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Scientists Warn of an 'Imminent' Stratospheric Warming Event Around The North Pole

Sudden stratospheric warming nudges frigid polar air from Siberia into Europe

Mike McRae

Every winter in the Northern Hemisphere, a cold wind circles the North Pole like water around a drain. It's an annual weather pattern meteorologists keep an anxious eye on – any significant changes could suggest Europe is in for a serious cold snap. Right now, that wind is ripping in two.

Researchers from the Universities of Bristol, Exeter, and Bath have come up with a new way to predict the knock-on effects of various changes to this major air current high up in the stratosphere, 10 to 50 kilometres (6 to 30 miles) overhead.

Ironically, the cause of this chill is a sudden burst of heat seeping into the whirling currents over a window of just 24 to 48 hours.

With its temperature surging by as much as 40 degrees Celsius, the vortex undergoes some rapid changes, changing course or dramatically breaking apart into daughter vortices that shove against surrounding atmosphere.

The results can be devastating. Just a few years ago, a sudden stratospheric warming (SSW) event nudged frigid polar air from Siberia into Europe, delivering a snow-laden cell of high pressure the media dubbed The Beast from the East.

Centred over Scandinavia, the shock of icy weather cast a frozen pall as far west as the UK, contributing to transport chaos and even a number of deaths.

That said, not all shifts in this polar vortex end in freezing conditions. Two years ago, warming of stratospheric polar winds preceded one of the warmest winter days in United Kingdom's recorded history.

Knowing which deviations are portents of winter fury, and which will fizzle, will go a long way in making weather forecasting more accurate.

Surprisingly, such stratospheric warming events themselves aren't exactly rare, with records suggesting an average of around half a dozen of them occur in the Arctic's polar vortex every decade.

"While an extreme cold weather event is not a certainty, around two thirds of SSWs have a significant impact on surface weather," says Richard Hall, University of Bristol meteorologist and lead author of the new study.

Observations dating back more than six decades have provided the researchers with 40 such examples of wobbles and splits in the northern stratospheric polar vortex, which inform a tracking algorithm that attempts to predict the impact each kind of change will have on weather systems across the northern hemisphere.

The results suggest any time the polar vortex splits into two smaller winds we can expect more severe cooling events, compared with other SSW anomalies.

It's a timely result, with forecast changes to the air currents appearing over the weekend.

"As predicted, atmospheric observations are now showing that the Arctic stratosphere is undergoing a sudden warming event associated with a weakening stratospheric polar vortex," says Adam Scaife, head of long-range prediction at the UK Met Office.

What's more, the change has all the hallmarks of the more dangerous kind of SSW, meaning there's a good chance that the predicted drop in temperature will be significant.

Having informed climate models certainly helps improve the odds of knowing what to expect. But while modelling on this scale benefits from improved algorithms, there's still room for plenty of uncertainty when it comes to nailing down the precise details in coming days.

Oddly, it might even turn out that Europe sweats instead of shivers.

The UK experienced record-setting winter warmth after a SSW in February 2019 after all, so the Met Office doesn't rule out the possibility of a similar swelter in coming weeks.

"Although the prolonged cold spell and snow events in February and March of 2018 – dubbed the 'Beast from the East' by the UK media – were linked to a sudden stratospheric warming, the record warm spell that occurred in February 2019 also followed such an event," says meteorologist Matthew Lehnert.

We've got some way to go before we can promise with confidence which way the weather will go in the wake of these polar changes.

But tools like this new algorithm will improve the odds of guessing, and continue to do so the more we learn about our atmosphere.

"Despite this advance many questions remain as to the mechanisms causing these dramatic events, and how they can influence the surface, and so this is an exciting and important area for future research," says mathematician William Seviour from the University of Exeter. This research was published in *JGR Atmospheres*.

http://bit.ly/2Xql4ni

A prognostic Alzheimer's disease blood test in the symptom-free stage

Memory deficit is a normal side effect of aging; at what point does memory loss become pathological?

Using a blood test, a German-Dutch research team has predicted the risk of Alzheimer's disease in people who were clinically diagnosed as not having Alzheimer's disease but who perceived themselves as cognitively impaired (Subjective Cognitive Declined, SCD). The researchers analyzed blood samples from an SCD cohort supervised at the Alzheimer Center Amsterdam. Using a test developed at Ruhr-Universität Bochum (RUB) called the Immuno-Infrared Sensor, they identified all 22 subjects at study entry who developed Alzheimer's dementia, thus the clinical symptoms, within six years. The test also showed which subjects were at very low risk to develop Alzheimer's dementia within six years. The team describes the results in the journal *Alzheimer's Research and Therapy*, published online 24 December 2020.

For the study, the team led by biophysics Professor Klaus Gerwert and Julia Stockmann of the Bochum Research Center for Protein Diagnostics (Prodi) collaborated with RUB statistician Professor Nina Timmesfeld, Department of Medical Informatics, Biometry and Epidemiology, and researchers from the Amsterdam University Medical Centers, Location Vrije University (VUmc) led by Professor Charlotte Teunissen and Professor Philip Scheltens.

Sensor detects misfolded proteins in blood

The SCD cohort included 203 individuals. At study entry, blood samples were taken from all the participants and analyzed using the patented immuno-infrared sensor that detects misfolding of the amyloid-beta (Aβ) peptide, which is a biomarker for Alzheimer's disease. In addition, the subjects underwent extensive Alzheimer's disease diagnostic testing; at study entry, this did not provide a

diagnosis of Alzheimer's disease in any of the subjects studied. The immuno-infrared sensor, on the other hand, detected misfolded Aβ peptides at study entry in all 22 subjects who developed the clinical disease in the following six years. In subjects who showed mild misfolding, it took on average longer (3.4 years) for conversion to clinical Alzheimer than in subjects with severe Aβ misfolding (2.2 years).

Together with statistician Nina Timmesfeld, the researchers predicted the risk of developing clinical Alzheimer's disease. According to the statistical model, SCD subjects with mild misfolding have an 11-fold higher risk and SCD subjects with severe misfolding have a 19-fold higher risk of developing clinical Alzheimer's in the following six years than subjects without misfolded Aβ peptide. "Misfolding of Aβ is therefore a very precise prognostic plasma biomarker," concludes Klaus Gerwert.

Combination of two biomarkers further improves prognosis

In addition, the team checked whether the combination of two different measurement methods in the plasma biomarker panel could further improve the prediction of disease risk. For this purpose, they combined the misfolding of all Aβ isoforms with a concentration decrease for Aβ42 as ratio to Aβ40 in plasma. The Amsterdam group measured Aβ concentrations using the new single-molecule array (SIMOA) technology. This increased the assay accuracy from an AUC (area under the ROC curve) of 0.94 to 0.99.

"We can now very accurately predict the risk of developing clinical Alzheimer's disease in the future, with a simple blood test on symptom-free individuals with subjective concerns," explains Klaus Gerwert. "However, we can just as confidently give the all-clear for SCD patients who have a very low probability of developing Alzheimer's disease in the next six years."

"Through the plasma biomarker panel, we can monitor disease progression over 14 years, beginning in the asymptomatic state with misfolding of Aβ and subsequent plaque deposition of Aβ42 in the brain associated with the first cognitive impairments," Julia Stockmann adds.

Hope for early-stage treatment

Such a blood test, which can detect the onset of Alzheimer's dementia even in the asymptomatic state, would be particularly useful if an active substance were available to treat the disease. In March 2021, the U.S. Food and Drug Administration will decide whether to approve the drug aducanumab. "Our results indicate that Alzheimer's drugs should be applied as early as possible in a non-clinical stage to improve therapy response," Klaus Gerwert said. The Bochum researcher is promoting the immuno-infrared sensor to be used in the selection of trial participants in the future to achieve a significantly better therapy response.

http://bit.ly/2LqVzmb

New strategy to fight world's most potent poison passes first tests in animals

Neutered forms of botulinum toxin chase their deadly counterpart into nerves and disarm it

By Kelly Servick

A new strategy to fight the world's most potent poison has passed its first tests in animals. Two research teams have developed neutered forms of botulinum toxin that chase their deadly counterpart into nerves and disarm it. The treatment, if it works in people, would be the first to reverse the paralyzing effects of the toxin inside cells and might spare patients long periods on a ventilator. "In a life-threatening situation, this will be very, very helpful," says Brenda Anne Wilson, a toxin microbiologist at the University of Illinois, Urbana-Champaign.

Made by bacteria that can grow in improperly preserved food and in infected wounds, the toxin penetrates motor nerves and hacks apart proteins critical for nerve signaling. “It’s not killing the neurons, but it silences them,” says Konstantin Ichtchenko, a biochemist at the New York University School of Medicine. In tiny quantities, botulinum toxin can control muscle spasms and relax wrinkles. But a larger dose can paralyze breathing.

Botulism is rare, with fewer than 200 U.S. cases logged per year, but the toxin is also a terrifying potential bioweapon. The current treatment, a cocktail of antibodies, can inactivate the toxin in blood, but can’t enter nerves. By the time symptoms emerge, some toxin is out of reach.

Now, Ichtchenko’s team and another led by Min Dong, a neuroscientist and microbiologist at Boston Children’s Hospital, have hitched neutralizing antibodies to a modified form of the toxin itself, which is adept at slipping into nerve cells. “We basically just created a Trojan horse,” Ichtchenko says.

Harnessing neurotoxins for drug delivery isn’t new, but using them to send in antibodies is “very intuitive and very elegant,” says Saak Ovsepian, a neurobiologist at the Czech Republic’s National Institute of Mental Health, whose team published a similar approach in 2011 using botulinum toxin to ferry gene-carrying viruses into neurons.

To devise its Trojan horse, Ichtchenko’s group made three genetic tweaks to a natural form of botulinum toxin that prevent it from slicing up cellular proteins. Dong notes, however, that the disarmed toxin can still cause muscle paralysis at high doses. So his study, headed by microbiologist Shin-Ichiro Miyashita, now at the Tokyo University of Agriculture, combined components of a disease-causing form with a related botulinum toxin that doesn’t naturally invade or disable human nerves. The resulting drug caused no toxicity in mice even at doses where a modified version of a common botulinum toxin was deadly.

Both teams linked their engineered toxin to a tiny antibody, derived from alpacas, that can inactivate the toxin. Compared with full-size antibodies, nanobodies can be more readily engineered to reach specific targets in cells and better keep their structure once inside, says Anne Messer, a molecular biologist at the Neural Stem Cell Institute.

Dong’s group injected mice with a lethal dose of botulinum toxin and administered its treatment 9 hours later—when paralysis had already set in. The 10 mice given the highest treatment dose were mobile within 6 hours, whereas untreated mice struggled to breathe and had to be euthanized, the team reports this week in *Science Translational Medicine*. In another set of experiments, the group linked the modified toxin to two different nanobodies and successfully disarmed two common varieties of botulinum toxin at once. In the same issue of the journal, Ichtchenko’s team describes successful tests in mice, guinea pigs, and macaque monkeys. All six monkeys given the treatment were alive 10 days after getting the toxin; none of seven untreated monkeys lived past 3.5 days.

James Marks, a molecular biologist at the University of California, San Francisco, notes that in contrast to lab animals that are given a single relatively small botulinum dose, human victims often have a large “reservoir” of toxin in their gut that enters the bloodstream over days or weeks. So even if this approach works, patients will likely also need the approved antitoxin treatment to remove toxin from the blood.

Both teams plan to refine their products and seek approval from the U.S. Food and Drug Administration, which can authorize drugs based on animal studies when human efficacy tests aren’t ethical. Experimental drugs face “a long, hard road” from animal results to an approved product, Marks says. “But this is where it starts.”

http://bit.ly/3hWWDaw

Producing milk from yeast that looks and tastes like cow's milk

Might a new technological development of researchers from Tel Aviv University soon revolutionize the dairy products we consume?

The initiators of the development believe that in the not-too-distant future we will be able to buy dairy products in the supermarket that are identical in taste and color to the ordinary dairy products that we consume today, but with one small difference: the dairy products will be produced from yeast rather than from cow.

Behind this development is Professor Tamir Tuller from the Biomedical Engineering Department of the Iby and Aladar Fleischman Faculty of Engineering at Tel Aviv University. Together with foodtech entrepreneur Dr. Eyal Iffergan, Tuller established the startup company Imagindairy, which attempts to do the as-yet impossible: produce cow's milk from yeast.

In recent years, increased awareness of the damage caused by the dairy industry to the environment and human health, and the ethical dilemmas of animal husbandry, biotechnology companies worldwide have been searching for milk substitutes. Professor Tuller explains that the goal of Imagindairy is to produce milk with all the important nutritional values of animal milk, and with the same taste, aroma, and texture that we are all familiar with, but without the suffering that cows endure, and without damage to the environment. Imagindairy's milk and cheese products will actually be much healthier than milk that comes from animals, since it will not contain cholesterol, lactose, or somatic cells.

"Our startup also includes food engineers and food experts from the Strauss Company," Professor Tuller says. "Currently, they are trying to take milk proteins from yeast and produce cheese from them. This is a long process of improvement—of productivity, taste, and, of course, of the price. This product is not a milk substitute like almond or soymilk. We plan to produce dairy products that will be identical to products that come from animals by introducing the yeast genome the genes that code for milk development in cows"

Imagindairy has been working with Tel Aviv University via Ramot, the university's technology transfer company, "The groundbreaking technology of Professor Tuller could revolutionize the dairy industry as we know it," said Keren Primor Cohen, the CEO of Ramot.

For about a decade, Professor Tuller's laboratory at Tel Aviv University has specialized in the modeling and engineering of gene expression using biophysical simulations, computational modeling of molecular evolution, and machine learning. Among other things, these models are used to make the production of heterologous proteins (proteins coded by genes that come from another organism) more efficient and thus cheaper. Professor Tuller's technology has been successfully used in the past to produce vaccines, antibodies, biosensors, and green energy using various organisms such as yeast, bacteria, micro-algae, and even viruses. Professor Tuller and his colleagues are now on the way to conquering a new objective: cow's milk.

Professor Tuller says: "The genome of every living creature contains genes that encode the recipe for making chains of amino acids that make up proteins. However, it also contains information that encodes the complicated process that is known as 'gene expression'—the timing and pace of the creation of the proteins. Gene expression is the process of turning information stored in "inanimate" DNA into proteins that are the 'essence of life' and are a major ingredient in every living thing that we know, from human beings to the coronavirus to cow's milk. For many years, biotechnology companies have been harnessing the gene expression process in order to produce desirable proteins affordably. They do

this by taking a gene from one living organism and implanting it in the genome of another organism that will serve as a 'factory' for producing the protein that is encoded in that gene. This technology has been used for many years to produce medications, vaccines, and energy, and it is also used in the food industry."

Professor Tuller adds: "Theoretically, we can reach a situation in which we can't tell the difference between cow's milk that comes from a cow and cow's milk that comes from yeast. But in order for that to happen in an economical way, we must turn the yeast cells into efficient factories that produce milk proteins—not a simple challenge to solve. Even though we know what the genes that encode the proteins for cow's milk are, those genes are written in the 'language' of cow cells, and need to be rewritten in the 'language' of yeast. This will make the production of the milk proteins possible in an appropriate, affordable, and efficient way in the yeast cell 'factory.'

With the help of models that we developed in the laboratory, we believe that within a fairly short time, we will succeed in making yeast produce milk proteins in an efficient way that will enable affordable, high-quality industrial-scale, production.

There have already been attempts to produce milk from microflora, but the price of producing milk in this way was a far cry from being affordable. I believe that we are on the right path, and within a fairly short time, we will be able to prepare in our own homes, toast with yellow cheese that was made from yeast and not from cow's milk, without having paid any more for it."

http://lat.ms/3bniwi9

Severe allergic reactions to Pfizer's COVID-19 vaccine are 'rare,' CDC says

Works out to 11.1 cases per 1 million doses

By Karen Kaplan

Severe allergic reactions to the COVID-19 vaccine made by Pfizer and BioNTech were "rare" in the first 10 days of its rollout across the country, according to a new report from the Centers for Disease Control and Prevention.

A total of 21 cases of anaphylaxis — none of them fatal — has been confirmed among nearly 1.9 million doses administered, CDC researchers wrote Wednesday in the Morbidity and Mortality Weekly Report. That works out to 11.1 cases per 1 million doses.

Anaphylaxis is a severe allergic reaction that can be triggered by a vaccine, as well as by food, medication, insect stings and latex. The reaction can be fatal if not treated immediately, typically with an injection of epinephrine to open airways in the lungs.

The reports of anaphylaxis and other side effects to the Pfizer-BioNTech vaccine were made to the Vaccine Adverse Event Reporting System (VAERS), which is maintained by the CDC and the Food and Drug Administration to keep track of safety issues once a vaccine is made available to the public.

Pfizer-BioNTech's COVID-19 vaccine was the first to receive emergency use authorization from U.S. regulators, and the first doses went into the arms of frontline healthcare workers Dec. 14. The new CDC report is based on 1,893,360 doses administered through Dec. 23.

Those doses resulted in 175 possible cases of severe allergic reactions. Investigators who reviewed those cases determined that 21 of them were anaphylaxis, and 86 were other allergic reactions. Sixty-one cases were not allergic reactions at all, and seven are still under review. Among the 21 people who suffered anaphylaxis, 17 had a history of allergies, including seven people who'd had anaphylactic reactions before.

Seventeen of the 21 patients were treated in emergency rooms and four patients were admitted to a hospital. Three of those hospitalized patients required intensive care.

Twenty of the patients had recovered by the time their cases were reported to the Vaccine Adverse Event Reporting System. Details about the 21st patient weren't known, but the CDC researchers noted that there have been no reports of anaphylaxis-related deaths linked to the Pfizer-BioNTech vaccine.

The 21 patients ranged in age from 27 to 60, with a median age of 40. Nineteen of them — or 90% — were women. The report authors noted that among cases where the sex of a vaccine recipient was known, 64% were women. They also pointed out that women were more likely to have an "immediate hypersensitivity" to the H1N1 influenza vaccine during the 2009 flu pandemic.

After receiving the COVID-19 vaccine, the fastest anaphylactic reaction came on after just two minutes, and the slowest appeared after 150 minutes. The overwhelming majority of reactions came quickly, with 15 happening within the first 15 minutes of the injection and three more occurring between 15 and 30 minutes.

Nineteen of the patients were treated with epinephrine.

The 21 cases were not clustered in any single geographic area, and they were tied to doses from multiple lots of the vaccine.

Among the other cases of allergic reactions, more than four out of five were considered "nonserious." The most common reactions reported to VAERS were rash or itchy skin, an itchy or scratchy throat, and mild respiratory symptoms. Half of these reactions occurred within 12 minutes of receiving the vaccine, and 90% of those who suffered them were women.

Overall, VAERS received 4,393 reports of adverse events of any kind during the first 10 days of the Pfizer-BioNTech vaccine rollout, according to the report. That's a rate of 0.2%.

The CDC has already updated its guidelines for administering the vaccine and a similar one developed by Moderna and the National Institutes of Health, which received emergency use authorization a week after the Pfizer-BioNTech product. **That guidance includes:**

- ***Make sure epinephrine is on hand and ready to use at vaccination sites.***
- ***Ask potential vaccine recipients about their history of allergic reactions to identify those at high risk.***
- ***Keep people under observation for up to 30 minutes after they receive the vaccine so that cases of anaphylaxis can be treated quickly.***
- ***Make sure that healthcare providers giving out the vaccine are trained to recognize the early signs of anaphylaxis.***
- ***Give an intramuscular injection of epinephrine immediately if anaphylaxis is suspected.***

The first doses of the Moderna vaccine were administered Dec. 21, and fewer than 225,000 doses had been given out during the 10-day period of this study. A separate report on its side effects is in the works, the CDC researchers said.

http://bit.ly/39koFZK

Protein that can be toxic in the heart and nerves may help prevent Alzheimer's

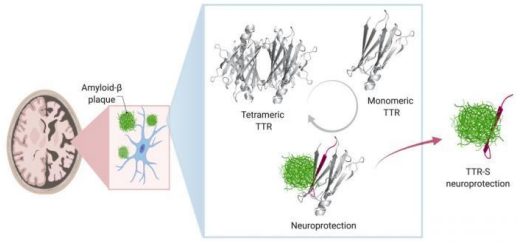
Can prevent the formation of toxic protein clumps associated with Alzheimer's disease

Dallas - A protein that wreaks havoc in the nerves and heart when it clumps together can prevent the formation of toxic protein clumps associated with Alzheimer's disease, a new study led by a UT Southwestern researcher shows. The findings, published recently in the *Journal of Biological Chemistry*, could lead to new treatments for this brain-ravaging condition, which currently has no truly effective therapies and no cure.

Researchers have long known that sticky plaques of a protein known as amyloid beta are a hallmark of Alzheimer's and are toxic to brain cells. As early as the mid-1990s, other proteins were discovered in these plaques as well.

One of these, a protein known as transthyretin (TTR), seemed to play a protective role, explains Lorena Saelices, Ph.D., assistant

professor of biophysics and in the Center for Alzheimer's and Neurodegenerative Diseases at UTSW, a center that is part of the Peter O'Donnell Jr. Brain Institute. When mice modeled to have Alzheimer's disease were genetically altered to make more TTR, they were slower to develop an Alzheimer's-like condition; similarly, when they made less TTR, they developed the condition faster.



Abnormal deposits of the protein amyloid beta in the brain have been linked to Alzheimer's disease. The above illustration reveals a potential way discovered by UTSW researchers to stop this process, leveraging the protective nature of the protein transthyretin (TTR) to identify a segment of this protein, TTR-S, that halts plaque formation and facilitates its degradation in a test tube. **UT Southwestern Medical Center**

In healthy people and animals, Saelices adds, TTR helps transport thyroid hormone and the vitamin A derivative retinol to where they're needed in the body. For this job, TTR forms a tetramer - a shape akin to a clover with four identical leaflets. However, when it separates into molecules called monomers, these individual pieces can act like amyloid beta, forming sticky fibrils that join together into toxic clumps in the heart and nerves to cause the rare disease amyloidosis. In this condition, amyloid protein builds up in organs and interferes with their function.

Saelices wondered whether there might be a connection between TTR's separate roles in both preventing and causing amyloid-related diseases. "It seemed like such a coincidence that TTR had such opposing functions," she says. "How could it be both protective and damaging?"

To explore this question, she and her colleagues developed nine different TTR variants with differing propensities to separate into monomers that aggregate, forming sticky fibrils. Some did this quickly, over the course of hours, while others were slow. Still others were extremely stable and didn't dissociate into monomers at all.

When the researchers mixed these TTR variants with amyloid beta and placed them on neuronal cells, they found stark differences in how toxic the amyloid beta remained. The variants that separated into monomers and aggregated quickly into fibrils provided some protection from amyloid beta, but it was short-lived. Those that separated into monomers but took longer to aggregate provided significantly longer protection. And those that never separated provided no protection from amyloid beta at all.

Saelices and her colleagues suspected that part of TTR was binding to amyloid beta, preventing amyloid beta from forming its own aggregations. However, that important piece of TTR seemed to be hidden when this protein was in its tetramer form. Sure enough, computational studies showed a piece of this protein that was concealed when the leaflets were conjoined could stick to amyloid beta. However, this piece tended to stick to itself to quickly form clumps.

After modifying this piece with chemical tags to halt self-association, the researchers created peptides that could prevent the formation of toxic amyloid beta clumps in solution and even break apart preformed amyloid beta plaques.

The interaction of modified TTR peptides with amyloid beta resulted in the conversion to forms called amorphous aggregates that were easily broken up by enzymes. In addition, the modified peptides prevented amyloid "seeding," a process in which fibrils of amyloid beta extracted from Alzheimer's disease patients can template the formation of new fibrils.

Saelices and her colleagues are currently testing whether this modified TTR peptide can prevent or slow progression of Alzheimer's in mouse models. If they're successful, she says, this

protein snippet could form the basis of a new treatment for this recalcitrant condition.

"By solving the mystery of TTR's dual roles," she says, "we may be able to offer hope to patients with Alzheimer's."

Other researchers who contributed to this study include Qin Cao, Daniel H. Anderson, Wilson Y. Liang, and Joshua Chou, all of the University of California, Los Angeles.

This work was supported by Amyloidosis Foundation grants 20160759 and 20170827 and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under Research Executive Agency (REA) Grant Agreement 298559.

http://wapo.st/3oteWa4

Why the search for the real origin of the coronavirus is a global concern

An upcoming World Health Organization mission to China intends to investigate the matter.

By Adam Taylor

Amid untold suffering, the coronavirus pandemic, which has killed at least 1.8 million people over the past year, has been an era of remarkable scientific breakthroughs, including record-breaking vaccine development programs.

But the answer to one of the fundamental questions about the virus remains shrouded in mystery: How did a pathogen found in bats make the jump to humans, presumably in or near the Chinese city of Wuhan, where it was first detected in late 2019?

An upcoming World Health Organization mission to China intends to investigate the matter.

That is, if it ever actually sets foot in China. WHO officials have been negotiating with Beijing to allow a team of international experts to investigate the virus's origin for almost a year, but Director General Tedros Adhanom Ghebreyesus said this week that China was still holding up the process.

In the void of information about the virus's origin, speculation has grown. Chinese officials have suggested that the virus might not have originated in their country, while U.S. officials have said repeatedly that the virus could have leaked from a lab in Wuhan.

In such a politicized and conspiratorial atmosphere, some virologists and public health experts now have doubts that a clear picture of the virus's origins can ever be discovered. But there are still reasons to hope that the WHO mission can proceed and succeed.

Search for the missing link

In interviews, the WHO team has emphasized that it does not intend to go into the mission with preconceived notions.

"Everything is on the table," Peter Ben Embarek, a Danish food safety expert and head of the mission, told my colleague Emily Rauhala during an interview last week. The team would begin with a "basic study that will give us clues, and those clues will then help us test different hypotheses."

Ben Embarek did say that one scenario would be the "least surprising" — that the virus now known as SARS-CoV-2, or the novel coronavirus, had spread from bats to an unidentified second animal before infecting humans through zoonotic spillover.

Among scientists, this is the apparent consensus. "The virus is just like a virus we would expect to see in wild bat populations, similar viruses have jumped from non-human animals to animals in the past, so I see no reason to speculate about this any further," Andrew Rambaut, a microbiologist at the University of Edinburgh, told Today's WorldView last year.

If it could be proved, this jump from a bat to another animal before humans could explain how the virus made it from the Chinese province of Yunnan, where scientists found its closest relative some time ago (a virus known as SARS-CoV RaTG13), to Wuhan, in Hubei province, more than 1,000 miles away.

But a key question remains: What, and where, was the intermediary animal? Without knowing the answer, scientists have fewer tools to

prevent the same thing from happening again. Around the world, experts have already seen that the virus can spread to and from animals including minks, prompting costly mass cullings.

The WHO team is expected to focus much of its investigation on the Huanan Seafood Market in central Wuhan, to which many early coronavirus cases were linked.

The delay in finding the animal in question is not without precedent. Ben Embarek noted that it took roughly a year to link Middle East respiratory syndrome, or MERS, to dromedary camels.

Sorting theory from fact

While most virologists favor the theory of zoonotic spillover, other, more controversial theories abound.

In recent weeks, for example, Chinese officials have pushed the idea that the virus came from outside the country.

High-level experts such as Wu Guizhen, biosafety expert at the Chinese Center for Disease Control and Prevention, have said that focusing on wildlife may be the wrong approach. "When we were investigating the origins of the virus, we kept looking for the intermediary host," Wu said in June. "Now, we may need to reexamine whether the virus really did come from wild animals."

Meanwhile, a rival theory suggests that the virus could have escaped from the Wuhan branch of the Chinese Center for Disease Control and Prevention, which did conduct research on bat coronaviruses.

That idea became popular among hawkish Republican lawmakers such as Sen. Tom Cotton (R-Ark.) last year, but it never really went away: As recently as last week, deputy national security adviser Matthew Pottinger was reported to have told British lawmakers that there was "a growing body of evidence" that this was a "a credible possibility."

The idea also gained mainstream prevalence with a recent New York Magazine story, which detailed the hypothesis that the virus had unintentionally leaked from the laboratory during controversial "gain of function" experiments, wherein viruses are manipulated to see how they can become more virulent and transmissible.

Virologists tend to be skeptical of both of these theories, noting that they come with political notions attached and that direct evidence for either is lacking.

The WHO team has pledged to consider them, but Ben Embarek said he had his doubts about both. The idea that the virus could have been imported to China a year ago was "not impossible but difficult," he said, while the leak theory was undermined by the fact that the virus was not among those in the lab's records.

A chance for cooperation

In an ideal world, global powers would come together to uncover the origins of the virus. The other theories need to be considered, cautiously, too. Even if the virus was not spread as a result of a "gain of function" experiment, its rapid spread raises questions about the risks involved in such experiments.

That's an issue that wouldn't just affect China: The United States previously blocked funding to similar experiments amid safety concerns, but resumed it in 2017.

But global efforts to understand the virus have not managed to transcend geopolitics. China has obfuscated international understanding of the virus's origins. The Associated Press reported last week that although hundreds of thousands of dollars in grants had been given out to those studying the origin of the virus, the publication of any of the findings was being tightly controlled by Chinese President Xi Jinping.

But the Trump administration has not made a cooperative effort on the issue either. Rather than support the effort for an international response to the pandemic, it pulled out of the WHO and escalated tensions with China. By placing political rivalry above scientific discovery, both China and the United States have undermined

research. Some experts think it is now unlikely that the WHO team will have the support to complete a credible investigation.

That would be a massive missed opportunity. As the WHO's own emergencies chief Mike Ryan said last week, the coronavirus is not the only pandemic humanity will face. "This is not necessarily the big one," he said.

http://bit.ly/2LuONs

Researchers uncover gut bacteria that can break down cholesterol

Treating high cholesterol by manipulating the gut microbiome could prevent cardiovascular disease

Raj Rajeshwar Malinda

You have probably read that high cholesterol can cause health problems, especially heart disease. Generally, a person's diet has been shown to have a direct impact on their cholesterol levels.

Recently, involvement of the gut microbiome has also been reported to regulate our cholesterol levels.

Now, researchers at MIT and Harvard University have uncovered one way that some gut bacteria can influence cholesterol. They found a group of bacteria that can produce a compound called *ismA*, which breaks down cholesterol. They found that people with these bacteria had lower cholesterol levels in their blood and fecal samples than people who lacked bacteria that can manufacture *ismA*. This finding may enable scientists to make new medications to manipulate cholesterol levels, or to treat people with high cholesterol with prebiotics to spur the growth of these cholesterol-digesting bacteria.

http://bit.ly/39hEHn7

Where antibiotic resistance comes from

Scientists have traced back the evolutionary history of antibiotic resistance genes

By comparing thousands of bacterial genomes, scientists in Gothenburg, Sweden have traced back the evolutionary history of antibiotic resistance genes. In almost all cases where an origin could be determined, the gene started to spread from bacteria that, themselves, can cause disease.

While human DNA is only passed down from parent to child, bacteria also have the habit of sharing some of their genes across species. This often applies to genes that make the bacteria resistant to antibiotics.

The use and overuse of antibiotics provide an advantage to those bacteria that have acquired resistance genes, thus further promoting the spread of resistance and making it more difficult to treat infections. This development threatens large parts of modern healthcare.

The rapid advances in DNA sequencing during the last decade has made it possible to study bacterial evolution much more effectively than ever before. This is an important background to the new study, published in the scientific journal Communications Biology.

The team from Gothenburg explored the scientific literature for claims of recent origins for antibiotic resistance genes, added information from public DNA-sequence-databases, and scrutinized the evidence at hand. While antibiotic-producing bacteria often are speculated to be the source for antibiotic resistance genes (as self-defence), this was not what the scientists found. None of the origin species found are known antibiotic producers. Strikingly, all verified origin species, except one, are known to cause disease, at least from time to time.

Professor Joakim Larsson, senior author of the study and director of the Centre for Antibiotic Resistance Research at University of Gothenburg, CARe, comments on the finding:

"Given that the overwhelming majority of bacteria are harmless to us, it was quite surprising that these genes almost exclusively came

from bacteria causing disease. On the other hand, it makes some sense since such bacteria often trigger antibiotic use when we become infected, and other pathogens are often nearby, ready to engage in gene-transfer. These findings underscores the microbial-rich gut flora humans and domestic animals given antibiotics as arenas for resistance evolution" he says.

Knowing where resistance genes come from can inform measures to delay the emergence of additional resistance genes in the clinics. Importantly, the authors conclude that the origin is still unknown for more than 95% of all known resistance genes.

"Most likely, most of them come from un-sequenced bacterial species. We know the majority of the species that frequently tend to reside in the gut or on the skin of ourselves and of domestic animals. Therefore, this points to an important role of a much less explored gene reservoir - the environmental microbiota. The role of the environment as a likely source for antibiotic resistance also stress the need reduce risks for resistance development in the environment, for example by limiting discharges of antibiotics though wastewaters", says Larsson.

Title: *A framework for identifying the recent origins of mobile antibiotic resistance genes, https://doi.org/10.1038/s42003-020-01545-5*

http://bit.ly/38tpPTx

This is how hominins adapted to a changing world 2 million years ago

Early hominins succeeded by being generalists with basic, versatile tools.

Kiona N. Smith

The versatility that helped humans take over the world emerged very early in our evolutionary history, according to sediments and stone tools from Olduvai Gorge in Tanzania.

Olduvai has provided some of the oldest known tools and fossils from our genus, *Homo*. A recent study lines that evidence up with environmental clues buried in the sediment. The results suggest that our early relatives were equipped to adapt to new environments by around 2 million years ago.

That seems to have been a key ability that allowed our relatives to go global. By 1.7 million years ago, an early human relative called *Homo erectus* had spread beyond Africa and throughout most of Asia, as far as Indonesia. They had reached western Europe by 1.2 million years ago. Along their travels, the hominins encountered environments very different from the ones their ancestors had evolved in, like the tropical forests of Indonesia and the arid steppes of central Asia.

They may have been able to prepare for that simply by staying in one place within Africa. At Ewass Oldupa, a recently excavated site on the edge of the famous Olduvai Gorge, findings indicate that early hominins lived in a constantly shifting landscape.

Life after the volcano

The oldest evidence we have for early human relatives at Olduvai Gorge is a handful of stone tools, made and used around 2.03 million years ago.

Like the other tools unearthed at Ewass Oldupa, they're part of the Olduwan complex: relatively simple stone tools made by early hominins like *H. erectus* and *H. habilis*. Olduwan tools are mostly sharp flakes and very basic tools for chopping, scraping and pounding. They're much less complex and precise than the tools made by later hominins, like Neanderthals, who chipped small flakes off carefully prepared stone cores. But for a few hundred thousand years, the rough-and-ready Olduwan tools got the job done.

At Ewass Oldupa, the job was survival in a landscape of mostly bracken fern meadows dotted with a few grasses and woody plants, watered by a meandering river. The ferns were probably the first plants to put down roots atop the wide fan of pumice that had

spewed from a nearby volcano not too long beforehand. Traces of that landscape are still buried in a layer of sediment about a meter above the rocky remains of the ancient pyroclastic flow; paleoanthropologist Michael Petraglia, of the Max Planck Institute for the Science of Human History, and his colleagues found fossilized pollen and microscopic pieces of fossilized plant tissue called phytoliths in the layer, alongside 10 stone tools.

For hunter-gatherers like *H. habilis*, whose fossilized remains have been unearthed just a few hundred meters away from Ewass Oldupa, the ferny basin would have been a pretty good place to make a living.

The river offered ready access to water, and the geology of the area provided several sources of stone for tools. Geochemical analysis of the tools at Ewass Oldupa suggest that hominins here gathered some of their quartzite locally and ventured up to 12 kilometers (7.5 miles) away for the rest. They seemed to choose different materials—in some cases as specific as choosing slightly different types of quartzite from different outcrops—for particular tools. (A study last year also suggested that the earliest toolmakers in our family tree knew enough to choose their materials wisely.)

But then, as it always does, everything changed.

New worlds in the same place

Thousands of years later, the hominins who had once foraged by the riverbanks wouldn't have recognized the landscape around Ewass Oldupa. The meadows of bracken had given way to a patchwork of woods and grasslands around the shores of a lake. Microscopic fossils trapped in the sediment suggest that the plant species that made up those woods and grasslands changed often, and deposits of charcoal reveal that wildfires periodically swept through the area, helping the patchwork landscape rearrange itself.

At other points in the area's long prehistory, the lake expanded, and the muddy sediments of the lakeshore hint at a lush landscape of forests and palm groves. The lakeshore later gave way to a dry steppe, mostly bare of trees and grass. Each of those environments offered wildly different foods, water, supplies, and challenges, but hominins seem to have kept coming back to Ewass Oldupa.

"Over the course of time, these habitats sometimes changed slowly or rapidly," Petraglia told Ars. "It is difficult to know how quickly hominins entered new ecosystems owing to the resolution of the record, but it is clear that they were able to cope with a wide variety of environments."

Petraglia and his colleagues found stone tools left behind by hominins who lived at the site (probably *H. habilis*) off and on throughout its 200,000 years of constant change. The 565 stone tools, scattered across millennia of layered sediment at the site, don't look like the detritus of a permanent settlement. Instead, it looks like hominins left the basin several times, maybe due to sudden environmental change or volcanic eruptions, but they kept coming back.

"There were a number of volcanic events within the 235,000 year time range represented at Ewass Oldupa," Petraglia told Ars. "It is interesting that hominins returned to these areas after each of the eruptions—that is, they never entirely abandoned the region."

Jacks of all trades

And even if the earliest hunters and gatherers at Ewass Oldupa would have found later versions of the place totally alien, they would still have recognized the tools people used to survive it. For roughly 200,000 years, hominins relied on the same basic tools to tackle the bracken meadows beside the river, the patchwork of woods and grassland, the lush lakeshore, and the dry steppe.

The chopping, scraping, and pounding tools of the Olduwan were relatively simple, but they were also incredibly versatile. According to Petraglia and his colleagues, Olduwan technology offered a basic, general toolkit that worked as well in a lakeside palm grove as it

did on a dry steppe. Humans took over the world because we're generalists, and generalists can adapt to nearly anything. Our early relatives clearly had the same advantage.

Nature Communications, 2020 DOI: 10.1038/s41467-020-20176 (About DOIs).

http://bbc.in/3sdYbBW

Two more life-saving Covid drugs discovered

Two more life-saving drugs have been found that can cut deaths by a quarter in patients who are sickest with Covid.

By Michelle Roberts

The anti-inflammatory medications, given via a drip, save an extra life for every 12 treated, say researchers who have carried out a trial in NHS intensive care units.

Supplies are already available across the UK so they can be used immediately to save hundreds of lives, say experts. There are over 30,000 Covid patients in UK hospitals - 39% more than in April.

The UK government is working closely with the manufacturer, to ensure the drugs - tocilizumab and sarilumab - continue to be available to UK patients.

As well as saving more lives, the treatments speed up patients' recovery and reduce the length of time that critically-ill patients need to spend in intensive care by about a week.

Both appear to work equally well and add to the benefit already found with a cheap steroid drug called dexamethasone.

Although the drugs are not cheap, costing around £750 to £1,000 per patient, on top of the £5 course of dexamethasone, the advantage of using them is clear - and less than the cost per day of an intensive care bed of around £2,000, say experts.

Lead researcher Prof Anthony Gordon, from Imperial College London, said: "For every 12 patients you treat with these drugs you would expect to save a life. It's a big effect."

In the REMAP-CAP trial carried out in six different countries, including the UK, with around 800 intensive care patients:

- ***Nearly 36% of intensive care Covid patients receiving standard care died***
- ***The new drugs reduced that by a quarter, to 27%, when given to patients within 24 hours of them entering intensive care***

Prof Stephen Powis, NHS national medical director, said: "The fact there is now another drug that can help to reduce mortality for patients with Covid-19 is hugely welcome news and another positive development in the continued fight against the virus."

Health and Social Care Secretary Matt Hancock said: "The UK has proven time and time again it is at the very forefront of identifying and providing the most promising, innovative treatments for its patients. "Today's results are yet another landmark development in finding a way out of this pandemic and, when added to the armoury of vaccines and treatments already being rolled out, will play a significant role in defeating this virus."

The drugs dampen down inflammation, which can go into overdrive in Covid patients and cause damage to the lungs and other organs.

Doctors are being advised to give them to any Covid patient who, despite receiving dexamethasone, is deteriorating and needs intensive care.

Tocilizumab and sarilumab have already been added to the government's export restriction list, which bans companies from buying medicines meant for UK patients and selling them on for a higher price in another country. The research findings have not yet been peer reviewed or published in a medical journal.

http://bit.ly/2XvnZLK

Dog Domestication May Have Begun because Paleo Humans Couldn't Stomach the Original Paleo Diet

Unable to digest large amounts of protein, hunters likely left scraps that could have led to the taming of wolves

By Rachel Nuwer

It's easy to understand why early humans domesticated dogs as their new best friends. Tame canines can guard against predators and interlopers, carry supplies, pull sleds and provide warmth during cold nights. But those benefits only come following domestication. Despite more than a century of study, scientists have struggled to understand what triggered the domestication process in the first place. A new theory described today in *Scientific Reports* posits that hunter-gatherers whose omnivorous digestive system prevented too much protein consumption likely shared surplus meat with wolves. Those scraps may have initiated a step toward domestication.

"This is the first time that we have an ecological explanation for dog domestication," says lead author Maria Lahtinen, a senior researcher at the Finnish Food Authority and a visiting scholar at the Finnish Museum of Natural History. "I personally don't think that there is a simple, easy answer behind dog domestication, but we need to see the full picture and complexity of the process."

Lahtinen did not originally set out to solve a long-standing dog mystery. Instead she was studying the diet of late Pleistocene hunter-gatherers in Arctic and sub-Arctic Eurasia. At that time, around 20,000 to 15,000 years ago, the world was engulfed in the coldest period of the last ice age. In frigid environments then, as today, humans tended to derive the majority of their food from animals. Nutritional deficiencies came from the absence of fat and carbohydrates, not necessarily protein. Indeed, if humans eat too much meat, diarrhea usually ensues. And within weeks, they can develop protein poisoning and even die. "Because we humans are not fully adapted to a carnivorous diet, we simply cannot digest protein very well," Lahtinen says. "It can be very fatal in a very short period of time."

During the coldest years of the last ice age—and especially in harsh Arctic and sub-Arctic winters—reindeer, wild horses and other human prey animals would have been eking out an existence, nearly devoid of fat and composed mostly of lean muscle. Using previously published early fossil records, Lahtinen and her colleagues calculated that the game captured by people in the Arctic and sub-Arctic during this time would have provided much more protein than they could have safely consumed.

In more ecologically favorable conditions, wolves and humans would have been competing for the same prey animals. But under the harsh circumstances of the Arctic and sub-Arctic ice age winter, sharing excess meat with canines would have cost people nothing. The descendants of wolves that took advantage of such handouts would have become more docile toward their bipedal benefactors over time, and they likely went on to become the first domesticated dogs. As the authors point out, the theory makes sense not just ecologically but also geographically: the earliest Paleolithic dog discoveries primarily come from areas that were very cold at the time.

The new study presents a "fascinating idea about lean protein being a food that humans would have discarded but wolves may have relied on during winter months in the Arctic," says Brian Hare, an evolutionary anthropologist at Duke University, who was not involved in the work. "I think it offers another vital clue for how the human-dog partnership might have been initially fueled."

http://bit.ly/39kXqXJ

This Is When You Should Work Out Each Day to Help Keep Weight Off, Study Suggests

To make the most of your exercise, you should do it at the same time each day

Mike McRae

Finding time to commit to exercise can be a real challenge, forcing many of us to squeeze in a quick run or gym session whenever there's a spare moment. But research suggests if you really want to

make the most of your exercise, you should do it at the same time each day. It's a schedule your body will thank you for.

A 2019 study lead by researchers from Brown Alpert Medical School in the US showed it really doesn't matter if you're a dawn jogger or a twilight cyclist; it's the consistency that's key if it's weight-loss you're after.

The US Department of Health and Human Services suggests two and a half hours of moderate physical activity each week is the least we should be doing to keep healthy.

And not just a minute here or there, but at least 10 minutes of heart-pounding exercise in each session.

Needless to say, if you're fairly fit and in a good state of health, you're probably meeting this requirement. But many of those who have problems keeping their weight down often struggle to get the exercise they need.

Using survey results on the physical activity of 375 individuals exercising for weight loss, the researchers of the 2019 study identified a strong relationship between a moderate-to-vigorous level of exercise at the same time of day and the amount of time spent exercising. Roughly half of the volunteers were morning people, which, when taken in context with a previous study by some of the same scientists, could indicate physical activity before you start your day is the way to go.

This preference for regularity might all come down to the way we think about our diary. Activities we expect to do at set times – such as picking up the kids, going to work, or attending social meetings – aren't really things we give a great deal of conscious thought to.

This mindless repetition is referred to as automaticity in psychology circles, and has already been shown to be important when it comes to sticking to an exercise regime. By actively considering how we could slot in a quick walk or treadmill session, we're more likely to cut back minutes of pulse-raising activity rather than commit to the exercise.

The secret is to therefore associate exercise with some pre-existing mental 'cue' for an appointment that you won't avoid, reducing the effort required if you had to plan an activity and then motivate yourself to see it through.

You might catch the 7:30 train, manage a short cardio workout at the gym near the office, and then be at your desk for that daily 9 am meeting. Or, if you're a night owl, going for a late run the moment you get home. That walk to the train station might be a habit, but it doesn't count. Incidental exercise can be worked into a routine, but only if it's of a kind that makes your heart noticeably pump harder and demands effort.

"Repeatedly exercising in the presence of consistent cues, such as at the same time of day or in the same location, may help to establish cue exercise relationships," wrote the researchers.

On its own, a survey such as this can only go so far in demonstrating what causes something as complicated as an exercise habit. Individual motivators can't be dismissed, and more research is needed before any definitive claims can be made.

"It will also be important to determine whether there is a specific time of day that is more advantageous for individuals who have initial low physical activity levels to develop a physical activity habit," the study's first author, Leah Schumacher, said in 2019.

Around the globe, just under a third of women and nearly a quarter of all men aren't engaging in a level of physical activity that will keep them on the right side of healthy. The reasons are no doubt complex and varied, and also seem to be linked with how much leisure time we actually have at our disposal.

It's hard, especially for busy folks, but getting your 150 minutes a week is important. Pick a time and stick to it.

This research was published in *Obesity*.

http://bit.ly/35vwj2l

Birds Have a Mysterious 'Quantum Sense'. For The First Time, Scientists Saw It in Action

Evidence of quantum physics directly affecting a biochemical reaction in a cell

Mike McRae

Seeing our world through the eyes of a migratory bird would be a rather spooky experience. Something about their visual system allows them to 'see' our planet's magnetic field, a clever trick of quantum physics, and biochemistry that helps them navigate vast distances.

Now, for the first time ever, scientists from the University of Tokyo have directly observed a key reaction hypothesised to be behind birds', and many other creatures', talents for sensing the direction of the planet's poles. Importantly, this is evidence of quantum physics directly affecting a biochemical reaction in a cell – something we've long hypothesised but haven't seen in action before.

Using a tailor-made microscope sensitive to faint flashes of light, the team watched a culture of human cells containing a special light-sensitive material respond dynamically to changes in a magnetic field. The change the researchers observed in the lab match just what would be expected if a quirky quantum effect was responsible for the illuminating reaction.

"We've not modified or added anything to these cells," says biophysicist Jonathan Woodward. "We think we have extremely strong evidence that we've observed a purely quantum mechanical process affecting chemical activity at the cellular level."

So how are cells, particularly human cells, capable of responding to magnetic fields?

While there are several hypotheses out there, many researchers think the ability is due to a unique quantum reaction involving photoreceptors called cryptochromes.

Cyrptochromes are found in the cells of many species and are involved in regulating circadian rhythms. In species of migratory birds, dogs, and other species, they're linked to the mysterious ability to sense magnetic fields.

In fact, while most of us can't see magnetic fields, our own cells definitely contain cryptochromes. And there's evidence that even though it's not conscious, humans are actually still capable of detecting Earth's magnetism.

To see the reaction within cyrptochromes in action, the researchers bathed a culture of human cells containing cryptochromes in blue light caused them to fluoresce weakly. As they glowed, the team swept magnetic fields of various frequencies repeatedly over the cells.

They found that each time the magnetic field passed over the cells, their fluorescence dipped around 3.5 percent – enough to show a direct reaction. So how can a magnetic field affect a photoreceptor?

It all comes down to something called spin – an innate property of electrons.

We already know that spin is significantly affected by magnetic fields. Arrange electrons in the right way around an atom, and collect enough of them together in one place, and the resulting mass of material can be made to move using nothing more than a weak magnetic field like the one that surrounds our planet.

This is all well and good if you want to make a needle for a navigational compass. But with no obvious signs of magnetically-sensitive chunks of material inside pigeon skulls, physicists have had to think smaller.

In 1975, a Max Planck Institute researcher named Klaus Schulten developed a theory on how magnetic fields could influence chemical reactions. It involved something called a radical pair.

A garden-variety radical is an electron in the outer shell of an atom that isn't partnered with a second electron.

Sometimes these bachelor electrons can adopt a wingman in another atom to form a radical pair. The two stay unpaired but thanks to a shared history are considered entangled, which in quantum terms means their spins will eerily correspond no matter how far apart they are.

Since this correlation can't be explained by ongoing physical connections, it's purely a quantum activity, something even Albert Einstein considered 'spooky'.

In the hustle-bustle of a living cell, their entanglement will be fleeting. But even these briefly correlating spins should last just long enough to make a subtle difference in the way their respective parent atoms behave.

In this experiment, as the magnetic field passed over the cells, the corresponding dip in fluorescence suggests that the generation of radical pairs had been affected.

An interesting consequence of the research could be in how even weak magnetic fields could indirectly affect other biological processes. While evidence of magnetism affecting human health is weak, similar experiments as this could prove to be another avenue for investigation. "The joyous thing about this research is to see that the relationship between the spins of two individual electrons can have a major effect on biology," says Woodward.

Of course, birds aren't the only animal to rely on our magnetosphere for direction. Species of fish, worms, insects, and even some mammals have a knack for it. We humans might even be cognitively affected by Earth's faint magnetic field.

Evolution of this ability could have delivered a number of vastly different actions based on different physics. Having evidence that at least one of them connects the weirdness of the quantum world with the behaviour of a living thing is enough to force us to wonder what other bits of biology arise from the spooky depths of fundamental physics. This research was published in *PNAS*.

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Now We Know Why Platypus Are So Weird - Their Genes Are Part Bird, Reptile, And Mammal

10 sex chromosomes, a pair of venomous spurs, a coat of fluorescent fur, and skin that 'sweats' milk

Carly Cassella

The first complete map of a platypus genome has just been released, and it's every bit as strange as you'd expect from a creature with 10 sex chromosomes, a pair of venomous spurs, a coat of fluorescent fur, and skin that 'sweats' milk.

Platypus eating a worm. **(JohnCarnemolla/Getty Images)**

The duck-billed platypus is truly one of the oddest creatures on Earth. Along with the spiky echidna, these two Australian animals belong to a highly-specialised group of mammals, known as monotremes, which both lay eggs but also nurse their young with milk.

The genes of both are relatively primitive and unchanged, revealing a bizarre blend of several vertebrate animal classes, including birds, reptiles, and mammals.

As different as the platypus might seem at first, it's those very differences that reveal our similarities and our shared ancestry with Earth's other vertebrates. Scientists think its genome could tell us secrets about our own evolution and how our distant mammalian ancestors went from laying eggs to giving birth.

"The complete genome has provided us with the answers to how a few of the platypus' bizarre features emerged," explains evolutionary biologist Guojie Zhang from the University of Copenhagen. "At the same time, decoding the genome for platypus is important for improving our understanding of how other mammals evolved - including us humans."

In previous years, a female platypus had some of its genome sequenced, but without any Y chromosome sequences, a lot of information was missing.

Using a male platypus, researchers have now created a physical map with a highly accurate platypus genome.

Today, living mammals are split into three groups, including monotremes, marsupials, and eutherians, or 'placentals'. We humans belong to that last group.

Together, the latter two make up a subclass known as therian mammals. Therian mammals all give birth to live young, but monotremes are simply too different to be lumped in with that group as well.

It's still unclear when all three of these distinct groups first began to diverge from one another. Some think the monotremes split off first, with marsupial and eutherians following suit. Others think all three groups diverged at roughly the same time.

The genome of the platypus has now helped clear up some of the dates. The data collected from echidna and platypus lineages suggests their last common ancestor lived up to 57 million years ago.

Meanwhile, monotremes as a whole appear to have diverged from marsupials and eutherian mammals about 187 million years ago.

Even after all that time, the semi-aquatic platypus has remained remarkably unchanged, fitting a niche in the Australian bush that many marsupials and mammals simply can't.

The authors were particularly interested in the animal's sex chromosomes, which appear to have originated independently from other therian mammals, all of which contain a simple XY pair.

The platypus, however, is the only known animal with 10 sex chromosomes (echidnas have nine). Platypus have 5X and 5Y chromosomes organised in a ring that appears to have broken apart into pieces over the course of mammalian evolution.

Comparing this chromosome information to humans, opossums, Tasmanian devils, chickens, and lizard genomes, the authors found the platypus's sex chromosomes have more in common with birds like chickens than mammals such as humans.

But while platypus lay eggs like chickens, they feed their young milk like therian mammals.

It's not too much of a surprise, therefore, that monotreme genomes contain most of the milk genes that other therian mammals possess.

Casein genes help encode certain proteins in mammalian milk, but monotremes appear to have extra caseins with unknown functions. That said, their milk is not unlike what comes from a cow, or even a lactating human.

As such, the platypus is probably not as dependent on egg proteins as other bird and reptile species because it can later feed their young through the lactation glands on its skin.

Its genome supports this. While birds and reptiles rely on three genes that encode for major egg proteins, the platypus appears to have lost the majority of these genes roughly 130 million years ago. Chickens today have all three egg protein genes, humans have none, and the platypus has only one fully functional copy left.

The platypus is a weird in-between, and its genome is a sort of bridge to our own evolutionary past.

"It informs us that milk production in all extant mammal species has been developed through the same set of genes derived from a common ancestor which lived more than 170 million years ago – alongside the early dinosaurs in the Jurassic period," Zhang says.

The full genome has also revealed the loss of four genes associated with tooth development, which probably disappeared roughly 120 million years ago. To eat, the platypus now uses a pair of horn-like plates to grind up its food.

The venomous spurs on its hind legs can possibly be explained by the creature's defensin genes, which are associated with the immune

system in other mammals, and appear to give rise to unique proteins in their venom. Echidnas, which also had their full genomes sequenced, appear to have lost this key venom gene.

The authors say their results represent "some of the most fascinating biology of platypus and echidna" alike.

"The new genomes of both species will enable further insights into therian innovations and the biology and evolution of these extraordinary egg-laying mammals," they conclude.

The study was published in *Nature*.

http://bit.ly/2K7OHqK

Evidence of water movement found in meteorites that only recently fell to Earth

Evidence of relatively recent water movement in meteorites

by Bob Yirka , Phys.org

A team of researchers affiliated with institutions in Australia, the U.S. and France has found evidence of relatively recent water movement in meteorites that only recently collided with the Earth. In their paper published in the journal *Science*, the group describes their study of carbonaceous chondrite (CC) meteorites that landed on the surface of the Earth within the past century and what they found.

A lot of scientists believe that the water present on Earth came from meteorites. This theory has been difficult to prove because the meteorites recovered to date do not contain water and because chemical reactions that might have involved comet-borne water occurred millions of years ago. In this new effort, the researchers took a look at the idea from another angle—they studied isotopes in meteorites that have landed on Earth over just the past century.

Prior research has suggested that most, if not all, CC meteorites were formed approximately 4.5 billion years ago as part of larger asteroids. To find out if recent arrivals might have evidence of a water history, the researchers looked at uranium and thorium distributions in samples—the former is water-soluble while the latter is not. Logic suggests that if water ever existed in the meteorite, it would have had to move as it melted, and that movement would be reflected in the distribution of thorium and uranium isotopes. Also, both isotopes have short half-lives, which means if their distributions in meteorites could be found, they would have occurred relatively recently—on the order of a few million years.

In studying nine of the meteorites, the researchers found the distributions they were looking for—a finding that suggested water had been moving due to melting, likely within the past 1 million years. The researchers suggest that not only could such meteorites have delivered water to Earth during the planet's formative years; they could also have been doing so in the much more recent past. They note that this idea could be tested by sampling asteroids before they strike the Earth, such as was done recently by Japanese and American spacecraft.

More information: *Simon Turner et al. Carbonaceous chondrite meteorites experienced fluid flow within the past million years, Science (2021). DOI: 10.1126/science.abc8116*

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Mutation in SARS-CoV-2 Variant Does Not Affect Vaccine: Study

An engineered coronavirus with the N501Y mutation—one of many mutations present in the emerging B.1.1.7 and 501.V2 variants of the coronavirus—is neutralized by the sera of COVID-19 vaccine recipients.

Kerry Grens

Serum samples from 20 individuals who received the Pfizer-BioNTech vaccine against SARS-CoV-2 thwarted a version of the coronavirus with the so-called N501Y mutation, according to a preprint posted to *bioRxiv* yesterday (January 7). This mutation is one of many sequence changes present in the B.1.1.7 and 501.V2

variants of SARS-CoV-2 that were first detected in the UK and South Africa, respectively, and are now rapidly spreading around the world.

"There's no reason to think the vaccines won't work just as well on these strains," Frederic Bushman of the University of Pennsylvania who tracks how the virus mutates and was not involved in the work, tells the Associated Press. But he adds that the study only examined one mutation and the B.1.1.7 and 501.V2 variants have many more mutations that were not tested.

N501Y resides within the coronavirus's spike protein that enables entry into host cells. Scientists at the University of Texas Medical Branch at Galveston had already engineered a version of SARS-CoV-2 with the N501Y mutation to study in mice when the new variants emerged, *The Washington Post* reports. The researchers collaborated with scientists at Pfizer to expose serum—an antibody-containing component of blood—from vaccine recipients to the engineered virus, and found no differences in neutralization between the N501Y virus and virus with the original Y501 sequence.

According to Reuters, Pfizer had challenged its vaccine against 15 other mutations previously, finding them all to be inconsequential. "So we've now tested 16 different mutations, and none of them have really had any significant impact. That's the good news," Philip Dormitzer, Pfizer's vice president and chief scientific officer of viral vaccines, tells Reuters. "That doesn't mean that the 17th won't."

In particular, scientists have expressed concern about a mutation in 501.V2 called E484K, which is next to be tested, Dormitzer tells the AP.

Coauthor Pei-Yong Shi of UTMB tells the *Post* he expects to receive a viral variant next week to study in the lab. Moderna, AstraZeneca, and other vaccine makers are also in the process of challenging their vaccines with the B.1.1.7 and 501.V2 variants. Bushman tells the AP he expects similarly positive results. "A mutation will change one little place, but it's not going to disrupt binding to all of them."

Nevertheless, vaccine developers have not ruled out the possibility that a variant could evolve that would require reformulating vaccines. "These data don't suggest a need for a change, but the mutations are hitting close enough to home that we need to be prepared," Dormitzer tells *STAT*.

http://bit.ly/3qa2igo

A 25-Year Study Just Identified 6 Distinct Types of Prediabetes

Based on shared biomarkers, including glucose levels, liver fat, body fat distribution, blood lipid levels, and genetic risk

David Nield

People with prediabetes have a higher than normal blood sugar level, and sometimes – but not always – go on to develop type 2 diabetes. Doctors should now be able to better manage that risk, thanks to a study identifying six different subtypes of prediabetes.

In an analysis covering 25 years of data and 899 individuals, researchers were able to categorise these six subtypes through a series of shared biomarkers, including glucose levels, liver fat, body fat distribution, blood lipid levels, and genetic risk.

The six subtypes (or "clusters") carry different levels of risk when it comes to developing type 2 diabetes, and that should help health professionals in tailoring treatments to match, as well as managing prediabetes and the secondary issues that come with it.

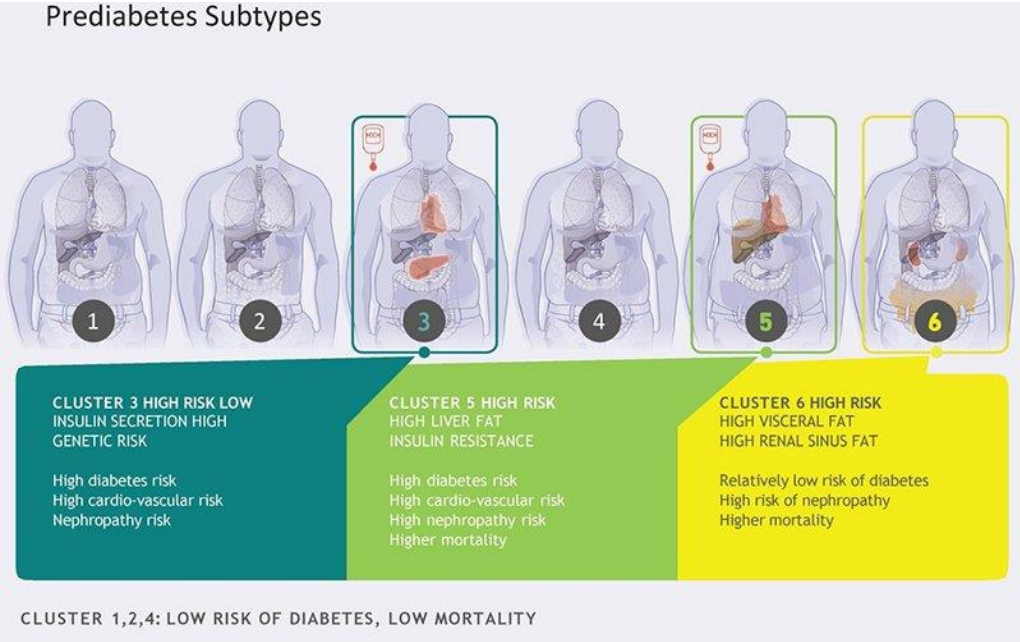
"For people with prediabetes it has not been possible until now to predict whether they would develop diabetes and be at risk for serious complications such as kidney failure, or whether they would only have a harmless form with slightly higher blood glucose levels but without significant risk," says medical researcher Hans-Ulrich

Häring from the German Centre for Diabetes Research (or DZD).

Clusters 1, 2 and 4 represent a low diabetes risk: they include participants who aren't overweight, or who are overweight but have a relatively healthy metabolism. Clusters 3, 5 and 6, meanwhile, are linked to an increased risk of diabetes and secondary diseases.

Those in cluster 3 produce too little insulin naturally, as well as showing other biomarkers such as higher intima-media thickness (IMT) in their arteries. Cluster 5 includes people more resistant to the effects of insulin and also with higher amounts of liver fat.

Those in cluster 6 have higher levels of particular types of body fat (visceral and renal sinus). While these individuals have a lower risk of developing diabetes compared with clusters 3 and 5, there is a higher mortality risk and more chance of kidney malfunction in this group.



(DZD)

"As in manifest diabetes, there are also different disease types in the preliminary stage of diabetes, which differ in blood glucose levels, insulin action and insulin secretion, body fat distribution, liver fat and genetic risk," said diabetologist Robert Wagner, from DZD.

To further verify their results, the researchers checked their data against an analysis of 6,810 records collected in the UK as part of a different project. The same subtypes or clusters were identified there, using similar markers and methods.

Knowing how people differ in terms of their likelihood of developing diseases, diabetes and complications make a big difference compared to lumping everyone together in the same prediabetes group-specific treatments can be given to specific risk groups.

With the number of people developing diabetes on the rise – worldwide there could be as many as 700 million individuals with type 2 diabetes by 2045 – and the condition already causing millions of deaths a year, it's important to act as fast as we can.

"Next, in prospective studies, we will first seek to determine to what extent the new findings are applicable for the classification of individual persons into risk groups," says diabetologist Andreas Fritsche, from DZD.

The research has been published in *Nature Medicine*.

http://bit.ly/2K9ADwY

High Pollen May Trigger Mysterious Flares of Chronic Bladder Pain in Some People

In people with a chronic pelvic condition, high pollen could also be triggering bouts of pelvic pain

Tessa Koumoundouros

Those of us with hay fever are painfully familiar with the frustration caused by days of high pollen – the incessant leaking of eye and nose mucus, itchy ears, eyes and throat, bursting fits of sneezes, and sometimes headaches and asthma. Now, a new study suggests that in people with a chronic pelvic condition, high pollen

could also be triggering bouts of pelvic pain.

More than 10 million people in the US live with the mysterious set of conditions known as urologic chronic pelvic pain syndrome (UCPPS) – a cluster of problems that include bladder pain syndrome and interstitial cystitis in women, chronic pelvic pain syndrome, and chronic prostatitis in men. They can cause debilitating symptoms like an urgent and frequent need to urinate, agony within the pelvic region, and painful sex.

Researchers have called UCPPS "one of the most frustrating urologic conditions to understand and manage" because its causes are still unknown as are its triggers of frustrating symptoms. A diagnosis of interstitial cystitis in women, for example, can involve bladder inflammation where all other possible known causes have been ruled out.

Everything from bacteria to psychological causes have been examined without much clarification.

However, case reports have suggested asthma and allergy medications can relieve UCPPS symptoms and patients have reported flare-ups coinciding with other allergies. So Washington University epidemiologist Siobhan Sutcliffe and colleagues decided to take a closer look at UCPPS's link with a well-known allergen.

The team compared 290 patient's flare-ups with pollen levels and found that while daily changes in pollen counts didn't seem connected, when pollen rates exceeded a "medium" threshold symptoms flared up by 22 percent one or two days later.

"Our study provides evidence to suggest increased pollen counts may trigger symptom flares in people living with UCPPS," said Sutcliffe.

The well-known process of mast cell activation in allergies that releases the histamines they carry is suspected to contribute to some of these UCPPS conditions. Animal studies have shown prolonged high levels of histamine in the bladder can make the bladder's nerves hypersensitive. And histamines in urine appear to remain elevated for longer than in our blood as our bodies use this exit pathway to remove them.

The new research adds to this evidence and could help provide patients with some much-needed relief. But further research is needed to account for possible confounding factors that may have been missed, such as other environmental factors that might coincide with higher pollen levels or things like flower bouquets which could contribute to flares.

"Patients may benefit from taking antihistamines on days with high pollen levels, or from allergy testing and immunotherapy," said Sutcliffe.

This study was published in *The Journal of Urology*.

http://bit.ly/3i0qZct

Megalodons gave birth to large newborns that likely grew by eating unhatched eggs in womb

Megalodons gave birth to babies larger than most adult humans

A new study shows that the gigantic Megalodon or megatooth shark, which lived nearly worldwide roughly 15-3.6 million years ago and reached at least 50 feet (15 meters) in length, gave birth to babies larger than most adult humans.

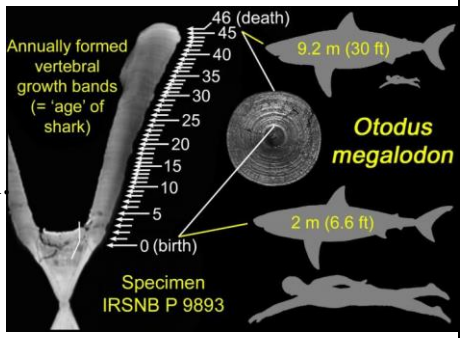
This latest research shedding light on the reproductive biology, growth and life expectancy of Megalodon (formally called Otodus megalodon) appears in the international journal *Historical Biology*.

Although Otodus megalodon is typically portrayed as a super-sized, monstrous shark in novels and films such as the 2018 sci-fi film "The Meg," scientific data support a more modest but still impressive estimate of about 50 feet (15 meters) for the presently known largest individuals. The study indicates that, from the moment of birth, Megalodon was already a big fish, noted Kenshu Shimada, a paleobiologist at DePaul University in Chicago and lead author of the study. Co-authors are Matthew Bonnan, Stockton

University, New Jersey; and Martin Becker and Michael Griffiths, William Paterson University, New Jersey.

"As one of the largest carnivores that ever existed on Earth, deciphering such growth parameters of O. megalodon is critical to understand the role large carnivores play in the context of the evolution of marine ecosystems," said Shimada.

Otodus megalodon has a rich fossil record, but its biology remains poorly understood like most other extinct sharks because the cartilaginous fish is primarily known only from its teeth. Nevertheless, some remains of gigantic vertebrae are known, said Shimada.



Identified annual growth bands in a vertebra of the extinct megatooth shark Otodus megalodon along with hypothetical silhouettes of the shark at birth and death, each compared with size of typical adult human. The vertebral specimen is housed in the Royal Belgian Institute of Natural Sciences in Brussels **DePaul University/Kenshu Shimada**

Large size at birth

Researchers used a CT scanning technique to examine incremental 'growth bands' putatively recorded annually (analogous to tree rings) in Megalodon vertebral specimen housed in the Royal Belgian Institute of Natural Sciences in Brussels. Measuring up to about 6 inches (15 centimeters) in diameter, the vertebrae were previously estimated to have come from an individual about 30 feet (9 meters) in length based on comparisons with vertebrae of modern great white sharks, according to the researchers.

CT images reveal the vertebrae to have 46 growth bands, meaning that the 9-meter Megalodon fossil died at age 46. By back-calculating its body length when each band formed, the research suggests that the shark's size at birth was about 6.6 feet (2 meters) in length, a result that suggests Megalodon gave live birth to possibly the largest babies in the shark world. These data also suggest that, like all present-day lamniform sharks, embryonic Megalodon grew inside its mother by feeding on unhatched eggs in the womb -- a practice known as oophagy, a form of intrauterine cannibalism.

"Results from this work shed new light on the life history of Megalodon, not only how Megalodon grew, but also how its embryos developed, how it gave birth and how long it could have lived," said co-author Becker.

Interestingly, 'early-hatched embryos' in the shark group called Lamniformes will begin to eat surrounding unhatched eggs, and at least in the present day sandtiger shark, occasionally even feed on other hatched siblings for nourishment, the researchers noted. The outcome is that only a few embryos will survive and develop, but each of them can become considerably large at birth.

Although likely energetically costly for the mother to raise such large embryos, newborns have an advantage because their large size reduces chances of being eaten by other predators, said Shimada.

"The information presented in this new paper and our other recent work demonstrating just how large Megalodon was relative to other sharks have greatly increased the understanding of the Megalodon biology," said co-author Griffiths.

Added co-author Bonnan, "My students and I examine spiny dogfish shark anatomy in class and to think that a baby Megalodon was nearly twice as long as the largest adult sharks we examine is mind-boggling."

Relatively steady growth after birth

The study also shows that the shark grew without significant 'growth spurts' at an average rate of about 6.3 inches (16 centimeters) per year at least during the first 46 years of its life according to the data. This finding indicates that Megalodon was sufficiently large (6.6 feet) at birth to compete with other predators

and to avoid being eaten. Further, a growth curve model based on the vertebrae appears to indicate its life expectance of at least 88-100 years, noted Shimada.

http://bit.ly/39p085Z

Study identifies exposure to common food-borne pathogen linked to rare brain cancer

Link between toxoplasma gondii (T. gondii) infection and the risk of glioma

Atlanta and Tampa, Fla. - A new study suggests a link between *toxoplasma gondii* (*T. gondii*) infection and the risk of glioma, a type of brain cancer, in adults. The report, appearing in the International Journal of Cancer, finds that people who have glioma are more likely to have antibodies to *T. gondii* (indicating that they have had a previous infection) than a similar group that was cancer free.

For the study, investigators led by James Hodge, JD, MPH and Anna Coghill, PhD examined the association between *T. gondii* antibodies measured several years before the cancer was diagnosed and the risk of developing a glioma. Study participants were from the American Cancer Society's Cancer Prevention Study-II (CPS-II) Nutrition Cohort and the Norwegian Cancer Registry's Janus Serum Bank (Janus). *T. gondii* is a common parasite that is most commonly acquired from undercooked meat, and may lead to the formation of cysts in the brain. These results suggest that reducing exposure to this common food-borne pathogen could provide a modifiable risk factor for highly aggressive brain tumors in adults.

Although glioma is a relatively rare disease, it is a highly fatal cancer. Globally in 2018, there were an estimated 300,000 incident cases and 241,000 deaths due to brain and other nervous system cancers. The majority (80%) of malignant brain tumors are gliomas, for which the estimated five-year relative survival rate is a stark 5%.

The study notes an association between *T. gondii* antibodies and glioma was similar in two demographically different groups of people: the CPS-II cases were approximately 70 years old at the time of blood draw, while those in the Janus cohort were approximately 40 years old.

"This does not mean that *T. gondii* definitely causes glioma in all situations. Some people with glioma have no *T. gondii* antibodies, and vice versa," notes Hodge.

"The findings do suggest that individuals with higher exposure to the *T. gondii* parasite are more likely to go on to develop glioma," said Coghill. "However, it should be noted that the absolute risk of being diagnosed with a glioma remains low, and these findings need to be replicated in a larger and more diverse group of individuals."

The authors note that, "if future studies do replicate these findings, ongoing efforts to reduce exposure to this common pathogen would offer the first tangible opportunity for prevention of this highly aggressive brain tumor."

Article: Hodge JM, Coghill AE, Kim Y, Bender N, Smith-Warner S, Gapstur S, Teras LR, Grimsrud TK, Waterboer T, Egan KM. Toxoplasma Gondii Infection and the Risk of Adult Glioma in Two Prospective Studies, 2021. International Journal of Cancer 2021; doi: 10.1002/ijc.33443.

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First human culture lasted 20,000 years longer than thought

Some 11 thousand years ago, Africa's furthest west harbored the last populations to preserve tool-making traditions first established by the earliest members of our species

Fieldwork led by Dr Eleanor Scerri, head of the Pan-African Evolution Research Group at the Max Planck Institute for the Science of Human History in Germany and Dr Khady Niang of the University of Cheikh Anta Diop in Senegal, has documented the youngest known occurrence of the Middle Stone Age.

This repertoire of stone flaking methods and the resulting tools includes distinctive ways of producing sharp flakes by carefully

preparing nodules of rock, some of which were sometimes further shaped into tool forms known as 'scrapers' and 'points.' Middle Stone Age finds most commonly occur in the African record between around 300 thousand and 30 thousand years ago, after which point they largely vanish.

Freshly found artefact from Laminia, Senegal **Credit: Eleanor Scerri**

It was long thought that these tool types were replaced after 30 thousand years ago by a radically different, miniaturized toolkit better suited to diversified subsistence strategies and patterns of mobility across Africa. In a paper published in *Scientific Reports* this week, Scerri and colleagues show that groups of hunter-gatherers in what is today Senegal continued to use Middle Stone Age technologies associated with our species' earliest prehistory as late as 11 thousand years ago. This contrasts with the long-held view that humanity's major prehistoric cultural phases occurred in a neat and universal sequence.

The 'Last Eden'?

"West Africa is a real frontier for human evolutionary studies - we know almost nothing about what happened here in deep prehistory. Almost everything we know about human origins is extrapolated from discoveries in small parts of eastern and southern Africa," says Dr Eleanor Scerri, the lead author of the study.

To redress this gap in the data, Scerri and Niang put together a research program to explore different regions of Senegal. The program ranges from Senegal's desert edges to its forests and along different stretches of its major river systems: the Senegal and the Gambia, where they found multiple Middle Stone Age sites, all with surprisingly young dates.

"These discoveries demonstrate the importance of investigating the whole of the African continent, if we are to really get a handle on the deep human past." says Dr Khady Niang. "Prior to our work, the story from the rest of Africa suggested that well before 11 thousand years ago, the last traces of the Middle Stone Age - and the lifeways it reflects - were long gone."

Explaining why this region of West Africa was home to such a late persistence of Middle Stone Age culture is not straightforward.

"To the north, the region meets the Sahara Desert," explains Dr Jimbob Blinkhorn, one of the paper's authors. "To the east, there are the Central African rainforests, which were often cut off from the West African rainforests during periods of drought and fragmentation. Even the river systems in West Africa form a self-contained and isolated group."

"It is also possible that this region of Africa was less affected by the extremes of repeated cycles of climate change," adds Scerri. "If this was the case, the relative isolation and habitat stability may simply have resulted in little need for radical changes in subsistence, as reflected in the successful use of these traditional toolkits."

"All we can be sure about is that this persistence is not simply about a lack of capacity to invest in the development of new technologies. These people were intelligent, they knew how to select good stone for their tool making and exploit the landscape they lived in," says Niang.

An ecological, biological and cultural patchwork

The results fit in with a wider, emerging view that for most of humanity's deep prehistory, populations were relatively isolated from each other, living in subdivided groups in different regions.

Accompanying this striking finding is the fact that in West Africa, the major cultural shift to more miniaturized toolkits also occurs extremely late compared to the rest of the continent. For a relatively short time, Middle Stone Age using populations lived alongside others using the more recently developed miniaturized tool kits, referred to as the 'Later Stone Age'.

"This matches genetic studies suggesting that African people living in the last ten thousand years lived in very subdivided populations," says Dr Niang. "We aren't sure why, but apart from physical distance, it may be the case that some cultural boundaries also existed. Perhaps the populations using these different material cultures also lived in slightly different ecological niches."

Around 15 thousand years ago, there was a major increase in humidity and forest growth in central and western Africa, that perhaps linked different areas and provided corridors for dispersal. This may have spelled the final end for humanity's first and earliest cultural repertoire and initiated a new period of genetic and cultural mixing.

"These findings do not fit a simple unilinear model of cultural change towards 'modernity'," explains Scerri. " Groups of hunter-gatherers embedded in radically different technological traditions occupied neighbouring regions of Africa for thousands of years, and sometimes shared the same regions. Long isolated regions, on the other hand, may have been important reservoirs of cultural and genetic diversity," she adds. "This may have been a defining factor in the success of our species."