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Studying human tumors in mice may end up being misleading

Tumors evolve to adapt to their new environment: a mouse.

John Timmer - 10/15/2017, 1:00 AM

Cancer is, unfortunately, governed by the same evolutionary rules that drive life itself. Cells in tumors are essentially competing to see which can divide the fastest. This competition drives them to pick up new mutations that can help them divide faster, survive immune attack, resist drugs, and expand to new areas of the body.

We can tell this by looking at the genetic changes that occur as tumors progress. Over time, we can trace the appearance of new mutations that confer abilities that are, from cancer's perspective, useful for tumor cells.

Now, a new study suggests that an unfortunate side effect of these evolutionary changes is that human tumors are really difficult to study. Whether the tumor cells are put in a culture dish or grown in mice, they evolve changes that help them grow in this new environment. And some of these changes influence how the tumor cells respond to drugs.

Options, all of them bad

It's possible to study cancer immediately after the removal of cells from a patient. But that only works for a limited amount of time. Instead, scientists have typically induced the cells to grow in a dish, surviving on a steady flow of nutrients delivered using a liquid medium. Some cancer cell lines have been maintained for decades using this approach.

Unfortunately, the approach is also limited. To begin with, a culture dish can't capture the complex interactions that cancer cells have with the normal cells around them or the immune system and metabolism of their host. In addition, some research has indicated that cells kept in culture pick up mutations that help them survive in a dish. To get around these issues, some researchers have started growing human cancer cells in mice. While this isn't the same as growing in a human (the mice are immunocompromised, to keep their immune system from killing the foreign cells), it's thought that this would provide an environment that better reflects what the cells would experience in a human body.

To an extent, that's probably true. But some researchers decided to see whether the mouse was an equivalent environment to the human body when it comes to the evolutionary pressures that the cancer cells face.

To do so, they focused on large changes in the genomes of the cancer cells—big duplications or deletions of DNA that encompass multiple genes. By altering the dose of several genes, these copy number changes alter the genes' activity with potential consequences for the cells' health. Copy number changes are also relatively easy to detect; the team used everything from genome sequencing to gene activity assays to determine when cells had gained or lost clusters of neighboring genes.

Tracking changes

To make comparisons, the researchers obtained samples from three different sources. One was a collection of tumors and metastases taken directly from a patient. A second was a set of tumor cells that had been grown in a culture dish. And, finally, they obtained tumor cells that had been grown in mice, in some cases transplanted to new mice as the original ones grew sick and had to be euthanized.

The most obvious result is that the cells underwent genetic changes in all of these environments. In some cases, the changes were similar. But in many others, there were changes that were distinct to each of the environments. In other words, some genetic changes aided tumor cell survival in humans but not in culture dishes or mice, and vice versa. These changes took place quickly. Over half of the tumor cell lines ended up with a large genetic change after spending time in one mouse. Nearly 90 percent of those that had been moved to another mouse four times picked up large changes. On average, these changes affected over 10 percent of the genome.

Strikingly, humans and mice caused selection of very different changes. For some tumors, growth and metastasis in humans favored the loss of specific genes, with their deletion present in the majority of tumor cells. In fact, as far as the researchers could tell, these genes had been completely lost from all cells. But apparently, they were still present in a small subpopulation, because the presence of the genes was favored in mice. After several transfers through mice, the majority of tumor cells had the genes in question.

In other cases, genes where extra copies were selected for being in humans vanished when grown in mice. All in all, opposite genetic changes in humans and mice (gain vs. loss of a gene or vice versa) were more common than cells experiencing similar changes in both organisms.

The big problem, however, is that some of these changes alter how the tumor cells respond to drugs. In other words, a drug that seems ineffective when tested in mice might actually work in the human patient in which the cells originated. Or a drug that works in mice might prove to be useless in the patient.

The fact that cancer cells will adapt to their environment isn't a surprise. The fact that a human and a mouse provide such strongly different environments, however, wasn't entirely expected. After all, people were using mice precisely because they were thought to provide a more realistic environment to study the tumor.

This doesn't mean that mice studies are useless; it just indicates they have to be treated with appropriate caution. And, since many researchers will continue to use this approach, it will provide us an opportunity to better understand the consequences of the genetic changes that occur when human cells are grown in mice. With a better grip on this biology, we might be able to make some inferences about which types of studies are likely to remain directly relevant to human health.

Nature Genetics, *2017. DOI: 10.1038/ng.3967 (About DOIs).*

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Whales and dolphins have rich 'human-like' cultures and societies

Whales and dolphins (Cetaceans) live in tightly-knit social groups, have complex relationships, talk to each other and even have regional dialects - much like human societies.

A major new study, published today in Nature Ecology & Evolution (Monday 16th October), has linked the complexity of Cetacean culture and behaviour to the size of their brains.

The research was a collaboration between scientists at The University of Manchester, The University of British Columbia, Canada, The London School of Economics and Political Science (LSE) and Stanford University, United States.

The study is first of its kind to create a large dataset of cetacean brain size and social behaviours. The team compiled information on 90 different species of dolphins, whales, and porpoises. It found overwhelming evidence that Cetaceans have sophisticated social and cooperative behaviour traits, similar to many found in human culture.

The study demonstrates that these societal and cultural characteristics are linked with brain size and brain expansion - also known as encephalisation. The long list of behavioural similarities includes many traits shared with humans and other primates such as:

complex alliance relationships - ***working together for mutual benefit***

social transfer of hunting techniques - ***teaching how to hunt and using tools***

cooperative hunting

complex vocalizations, including regional group dialects - ***'talking' to each other***

vocal mimicry and 'signature whistles' unique to individuals - ***using 'name' recognition***

interspecific cooperation with humans and other species - ***working with different species***

alloparenting - ***looking after youngsters that aren't their own***

social play

Dr Susanne Shultz, an evolutionary biologist in Manchester's School of Earth and Environmental Sciences, said: "As humans, our ability to socially interact and cultivate relationships has allowed us to colonise almost every ecosystem and environment on the planet. We know whales and dolphins also have exceptionally large and anatomically sophisticated brains and, therefore, have created a similar marine based culture.

"That means the apparent co-evolution of brains, social structure, and behavioural richness of marine mammals provides a unique and striking parallel to the large brains and hyper-sociality of humans and other primates on land. Unfortunately, they won't ever mimic our great metropolises and technologies because they didn't evolve opposable thumbs."

The team used the dataset to test the social brain hypothesis (SBH) and cultural brain hypothesis (CBH). The SBH and CBH are evolutionary theories originally developed to explain large brains in primates and land mammals.

They argue that large brains are an evolutionary response to complex and information-rich social environments. However, this is the first time these hypotheses have been applied to 'intelligent' marine mammals on such a large scale.

Dr Michael Muthukrishna, Assistant Professor of Economic Psychology at LSE, added: "This research isn't just about looking at the intelligence of whales and dolphins, it also has important anthropological ramifications as well. In order to move toward a more general theory of human behaviour, we need to understand what makes humans so different from other animals. And to do this, we need a control group. Compared to primates, cetaceans are a more "alien" control group."

Dr Kieran Fox, a neuroscientist at Stanford University, added: "Cetaceans have many complex social behaviours that are similar to humans and other primates. They, however, have different brain structures from us, leading some researchers to argue that whales and dolphins could not achieve higher cognitive and social skills. I think our research shows that this is clearly not the case. Instead, a new question emerges: How can very diverse patterns of brain structure in very different species nonetheless give rise to highly similar cognitive and social behaviours?"

http://bit.ly/2qwMVAE

Predictions by GSI scientists now confirmed

Heavy elements in neutron star mergers detected

On October 16 a team of scientists, including members from the LIGO and Virgo collaborations and several astronomical groups, announced the detection of both gravitational and electromagnetic waves, originating from the merger of two neutron stars. These mergers have been speculated as the yet unknown production site of heavy elements including Gold, Platinum and Uranium in the Universe. In 2010 an international collaboration led by Gabriel Martínez-Pinedo (GSI Helmholtzzentrum für Schwerionenforschung and Technische Universität Darmstadt) and Brian Metzger (Columbia University) pointed out that the heavy element synthesis in the merger process leads to a unique electromagnetic wave emission pattern.

The electromagnetic signal observed from the merging neutron stars indeed shows this pattern and confirms that the site for the heavy element production in the Universe is finally found, solving one of the 11 most important question in physics, as named by the US National Academies in 2003. This breakthrough puts even further focus on the Facility for Antiproton and Iron Research (FAIR), which is currently being built in Darmstadt and at which the short-lived and very neutron-rich nuclei which drive the observed electronmagnetic signal will be produced and studied for the first time.

60 years ago the main processes responsible for the production of elements in the Cosmos were outlined. Since then, it has been possible to identify the astrophysical sites for most of those processes except for the so called r process that is responsible for producing half of the elements heavier than Iron. It requires an environment with extreme

neutron densities, permitting neutron captures on nuclei to proceed much faster than beta-decays. „Identifying the site of the astrophysical origin of elements heavier than Iron is viewed as one of the Millenium problems in physics" says Friedrich-Karl Thielemann, Professor at the University of Basel and now also member of the GSI theory group, who in 1999 performed the first nucleosynthesis study showing that the r-process can operate in material ejected during the coalescence of two merging neutron stars.

Almost simultaneously, it was suggested that the radioactive decay of the freshly synthesized nuclei will trigger an electromagnetic transient. The first realistic modeling of the electromagnetic signal was performed in 2010 by an international team led by Gabriel Martinez-Pinedo and Brian Metzger, including Almudena Arcones, GSI and Technische Universität Darmstadt, and key experimental guidance from GSI scientists Aleksandra Kelic-Heil and Karl-Heinz Schmidt. They predicted that such an event will be a thousand times brighter than a nova and will reach its maximum on timescales of a day. It was named "kilonova". This picture has been confirmed by the recent observation of an optical/infrared counterpart associated with GW170817. This represents a unique case in nuclear astrophysics, as usually astronomers observe a new phenomenon which is much later explained by theorists. In the present case we anticipated a novel astronomical signal without the benefit of observational guidance much before it was confirmed by observations", says Gabriel Martinez-Pinedo.

Several signatures point to the radioactive decay of r-process nuclei to explain the observations. The time dependence of the signal corresponds to what is expected assuming that the energy is produced from the decay of a large ensemble of radioactive nuclei. Furthermore, the evolution in color of the signal shows that a broad range of r-process nuclei has been produced from the lighter elements with Z ~ 50 to the heavier with Z ~ 82. It has been estimated that GW170817 produced around 0.06 solar masses of r-process ejecta with over ten times Earth's mass in Gold and Uranium.

The LIGO and Virgo collaborations predict that once the gravitational wave detectors reach the design sensitivity in 2019 we may be able to detect neutron star mergers as frequently as once per week. This will represent a complete change of paradigm in our understanding of heavy element nucleosynthesis demanding high precision nuclear data, in particular of heavy neutron-rich nuclei to reproduce the observations.

It is very fortunate that with FAIR the facility needed to provide these data is already under construction in Darmstadt. First results are expected from experiments performed in the FAIR phase-0 starting 2018. Once FAIR reaches its complete potential in 2025, it will offer unique physics opportunities to determine the properties of heavy neutron-rich nuclei of relevance to r-process nucleosynthesis. In the meantime, it is the aim of the GSI theory group to identify key nuclear information to fully characterize the variety of electromagnetic transients expected from neutron star mergers.

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Many pelvic tumors in women may have common origin -- fallopian tubes

Most - and possibly all - ovarian cancers start, not in ovaries, but instead in the fallopian tubes attached to them.

This is the finding of a multicenter study of ovarian cancer genetics led by researchers from Perlmutter Cancer Center at NYU Langone Health, and published online Oct. 17 in Nature Communications.

"Based on a better understanding of its origins, our study suggests new strategies for the prevention and early detection of ovarian cancer," says senior study author Douglas A. Levine, MD, director of the Division of Gynecologic Oncology at Perlmutter and professor of Obstetrics and Gynecology at NYU School of Medicine.

The results revolve around the fallopian tubes, which enable egg cells that have the potential to be fertilized and become embryos - to pass

from the ovaries where they are made to the uterus. The new study found that ovarian cancer cells have more in common with cells covering the tips of fallopian tubes than with those on the surface of ovaries.

If biomarkers can be found for these tubal cells, say the authors, future blood tests, advanced Pap smears, or direct tests on tubal tissue might be able to detect ovarian cancer earlier. The research team plans to conduct studies that will seek to apply the current molecular biology findings to clinical practice, but Levine says it may take years to prove that this approach detects ovarian cancer earlier, prevents its spread, or extends survival in patients with this disease.

The new findings also point to the possibility that removing a woman's fallopian tubes, but not her ovaries, may reduce risk of ovarian cancer in those at high risk for disease, including those with genetic changes (mutations) known to increase risk (e.g. BRCA).

"We are one of several centers taking part in Women Choosing Surgical Prevention or WISP trial, which seeks to determine whether removing the tubes improves quality of life, compared to removing both the tubes and ovaries," Levine says.

Also not yet clear is whether or not the cells that become ovarian cancer become malignant in the fallopian tubes or if they circulate to other organs first. If it is the latter, then removing the fallopian tubes might not work. It is also possible that some ovarian cancers originate elsewhere, says Levine.

Despite the remaining uncertainties, the current study does confirm previous results that had suggested that many high-grade serious cancers in the pelvis are preceded by abnormal cells (lesions) occurring in the fallopian tubes, called serous tubal intraepithelial carcinoma (STIC).

Past studies in several cancer types had shown that cancer cells with different origins have different genetic profiles. Cancer cells may arise from nearby tissue or may have spread to a location from another part of the body, but their genetic profile reflects the tissue of origin.

Thus, the researchers knew going in that if STIC cells and ovarian cancer cells had different genetic profiles, they must have originated in different tissue types. Instead, in-depth molecular analyses of cells from 96 women with high-grade serous carcinoma failed to identify any genetic differences between cancer cells arising in the tubes and serous "ovarian" cancers occurring elsewhere in the pelvis.

"We found no differences in the 20,000 genes that we can identify," says Levine. "This leads us to believe that that these ovarian cancers all originate in the fallopian tubes."

Ovarian cancer is more aggressive than many other cancers because it is hard to diagnose in its earliest - and most treatable - stages. Fewer than 50 percent of women diagnosed with the disease survive for longer than five years after their diagnoses, according to the American Cancer Society.

In addition to Levine, co-authors of the study were Fanny Dao and Narciso Olvera of NYU School of Medicine; Jennifer Ducie of Mercy Medical Center in Baltimore; Patricia Shaw of University Health Network in Toronto; Michael Considine, Leslie Cope, Robert Kurman and le-Ming Shih of Johns Hopkins Medical Institutions in Baltimore; and Robert Soslow of Memorial Sloan Kettering Cancer Center in New York. Funding for the study was provided by Arnold Chavkin and Laura Chang, the Chia Family Foundation, Department of Defense CDMRP Grant W81XWH-11-2-0230, and National Cancer Institute grant P30CA008748.

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Keratin, proteins from 54-million-year-old sea turtle show survival trait evolution

Original pigment, beta-keratin and muscle proteins from a 54 million-year-old sea turtle hatchling

Researchers from North Carolina State University, Lund University in Sweden and the University of Hyogo in Japan have retrieved original pigment, beta-keratin and muscle proteins from a 54 million-year-old sea turtle hatchling. The work adds to the growing body of evidence supporting persistence of original molecules over millions of years and also provides direct evidence that a pigment-based survival trait common to modern sea turtles evolved at least 54 million years ago.

Tasbacka danica is a species of sea turtle that lived during the Eocene period, between 56 and 34 million years ago. In 2008 an extremely

well-preserved T. danica hatchling was recovered from the Für formation in Jutland, Denmark. The specimen was less than 3 inches (74 millimeters) long. In 2013 paleontologist Johan Lindgren of Lund University uncovered soft tissue residues from an area located near the sea turtle's left "shoulder." He collected five small samples for biomolecular analysis.

The shells of modern sea turtle hatchlings are dark colored - this pigmentation gives them protection from aerial predators (such as seagulls) as they float on the ocean surface to breathe. Since turtles are reptiles, and therefore cold-blooded, the dark coloration also allows them to absorb heat from sunlight and regulate their body temperature. This elevated body temperature also allows more rapid growth, reducing the time they are vulnerable at the ocean surface.

The T. danica hatchling specimen appeared to share this coloration with its living counterparts. The researchers observed round organelles in the fossil that could be melanosomes, pigment-containing structures in the skin (or epidermis) that give turtle shells their dark color.

To determine the structural and chemical composition of the soft tissues Lindgren collected and see if the fossil sea turtle did have a dark colored shell, the researchers subjected the sample to a selection of high-resolution analytical techniques, including field emission gun scanning electron microscopy (FEG-SEM), transmission electron microscopy (TEM), in situ immunohistochemistry, time-of-flight secondary ion mass spectrometry (ToF-SIMS), and infrared (IR) microspectroscopy.

Lindgren performed ToF-SIMS on the samples to confirm the presence of heme, eumelanin and proteinaceous molecules - the components of blood, pigment and protein.

Co-author Mary Schweitzer, professor of biological sciences at NC State with a joint appointment at the North Carolina Museum of Natural Sciences, performed histochemical analyses of the sample, finding that it tested positive against antibodies for both alpha and beta-keratin, hemoglobin and tropomyosin, a muscle protein. TEM, performed by University of Hyogo evolutionary biologist Takeo Kuriyama, and Schweitzer's immunogold testing further confirmed the findings.

In the end, the evidence pointed to these molecules as being original to the specimen, confirming that these ancient turtles shared a pigmentation-based survival trait with their modern-day brethren.

"The presence of eukaryotic melanin within a melanosome embedded in a keratin matrix rules out contamination by microbes, because microbes cannot make eukaryotic melanin or keratin," Schweitzer says. "So we know that these hatchlings had the dark coloration common to modern sea turtles.

"The data not only support the preservation of multiple proteins, but also suggest that coloration was used for physiology as far back as the Eocene, in the same manner as it is today."

The paper, "Biochemistry and adaptive colouration of an exceptionally preserved juvenile fossil sea turtle," appears in Scientific Reports. Lindgren is first and corresponding author. The work was funded in part by the National Science Foundation (ECCS-1542015 and EAR-1344198). "Biochemistry and adaptive colouration of an exceptionally preserved juvenile fossil sea turtle" DOI: 10.1038/s41598-017-13187-5

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Published: Oct. 17 online in Scientific Reports

Abstract:

The holotype (MHM-K2) of the Eocene cheloniine Tasbacka danica is arguably one of the best preserved juvenile fossil sea turtles on record. Notwithstanding compactional flattening, the specimen is virtually intact, comprising a fully articulated skeleton exposed in dorsal view. MHM-K2 also preserves, with great fidelity, soft tissue traces visible as a sharply delineated carbon film around the bones and marginal scutes along the edge of the carapace. Here we show that the extraordinary preservation of the type of T. danica goes beyond gross morphology to include ultrastructural details and labile molecular components of the once-living animal. Haemoglobin-derived compounds, eumelanic pigments and proteinaceous materials retaining the immunological characteristics of sauropsid-specific β-keratin and tropomyosin were detected in tissues containing remnant

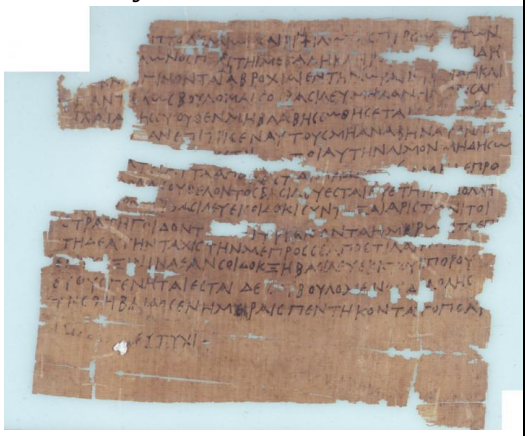
melanosomes and decayed keratin plates. The preserved organics represent condensed remains of the cornified epidermis and, likely also, deeper anatomical features, and provide direct chemical evidence that adaptive melanism - a biological means used by extant sea turtle hatchlings to elevate metabolic and growth rates - had evolved 54 million years ago.

http://bit.ly/2ipsUwq

Volcanic eruptions linked to social unrest in Ancient Egypt

Strong case that sudden shifts in climate can have big impacts on human society

Around 245 BCE Ptolemy III, ruler of the Ptolemaic Kingdom in Egypt, made a decision that still puzzles many historians: After pursuing a successful military campaign against the kingdom's nemesis, the Seleucid Empire, centred mainly in present-day Syria and Iraq, Ptolemy III suddenly decided to return home. This about-face "changed everything about Near-East history," says Joseph Manning, a historian at Yale University.



This piece of papyrus from the mid-Third Century BCE describes a period of famine in Egypt that occurred when the Nile River failed to flood for several years in a row. It was collected from the Egyptian city of Edfu. **© Department of Papyrology, Institute of Archaeology, University of Warsaw**

Now, Manning and his colleagues have identified a possible reason for Ptolemy III's trek back to Egypt: volcanoes. It's a strange link, but one borne out by evidence. Massive eruptions, a new study suggests, can disrupt the normal flow of the Nile River by cooling the planet's atmosphere. In Ancient Times, that may have led to food shortages and heightened existing tensions in the region. The research, which will be published on Tuesday, 17 October in Nature Communications, links eruptions not just to the end of Ptolemy III's war, but to a series of violent uprisings and other upheavals that rocked Ptolemaic Egypt - an empire that extended over large portions of Northeast Africa and the Middle East.

The study creates a strong case that sudden shifts in climate can have big impacts on human society. And it's remarkable, Manning says, for doing so by drawing on a wide range of methods and evidence - from ice core records to Egyptian papyri.

"That's the beauty of these climate records. For the first time, you can actually see a dynamic society in Egypt, not just a static description of a bunch of texts in chronological order," Manning says. "This is of absolutely enormous importance."

This research is a product of the Volcanic Impacts on Climate and Society working group of Past Global Changes (PAGES), a global research project of Future Earth.

At the heart of that dynamic society was the Nile River, the lifeblood of the Ptolemaic Kingdom. This empire arose in about 305 BCE, not long after the death of Alexander the Great, and ended around 30 BCE with the death of Cleopatra. During this period, Egyptian farmers depended on the yearly flooding of the Nile in July through September to irrigate their grain fields - inventing systems of channels and dams to store the river's overflow.

"When the Nile flood was good, the Nile valley was one of the most agriculturally-productive places in the Ancient World," says Francis Ludlow, a climate historian at Trinity College in Dublin and a co-author of the new study. "But the river was famously prone to a high level of variation."

In some years the Nile didn't rise high enough to flood the land, and that could lead to trouble. Historical records suggest, for example, that a shortage of grain and the unrest that followed were behind Ptolemy III's return to Egypt. And Ludlow had reason to think that volcanoes could be behind some of those bad years.

The reason comes down to a squiggly band of monsoon weather that circles the planet's equator called the intertropical convergence zone

(ITCZ). Every year around summer in the northern hemisphere, this band moves up from the equator. That, in turn, soaks the headwaters of the Blue Nile River, a major tributary of the Nile. But when volcanoes erupt, they blast out sulfurous gases that, through a chain of events, cool the atmosphere. If that happens in the Northern Hemisphere, it can keep the monsoon rains from moving as far as they usually do.

"When the monsoon rains don't move far enough north, you don't have as much rain falling over Ethiopia," Ludlow says. "And that's what feeds the summer flood of the Nile in Egypt that was so critical to agriculture."

But how often would eruptions diminish the river's flooding? To find out, Ludlow, Manning and their colleagues turned to computer simulations and real-world measurements of the Nile River that date back to 622 CE. The team discovered that poor flood years on the Nile lined up over and over with a recently published timeline of major volcanic eruptions around the world. That evidence suggested that when volcanoes explode, the Nile tended to stay calm.

The team then dug further to see if that might have an impact on Egyptian society during the Ptolemaic era, which is rich in papyri and other written records. They include the trilingual Rosetta Stone. Again, the timelines matched: Volcanic eruptions preceded many major political and economic events that affected Egypt. They included Ptolemy III's exit from Syria and Iraq - just after a major eruption in 247 BCE - and the Theban revolt, a 20-year uprising by Egyptians against Greek rule. The researchers then examined how likely it was that these events occurred so close in time to eruptions, finding it "highly unlikely to have occurred by chance, such is the level of overlap," Ludlow says.

The volcanic eruptions didn't cause these upheavals on their own, both Ludlow and Manning stress. But they likely added fuel to existing economic, political and ethnic tensions. For historians, "it's like we've all been in a dark room bumping into furniture, and now we have a candle lit," Manning says.

The results may also have implications for the modern era. Currently, Ethiopia is in the middle of building a humongous dam called the Grand Ethiopian Renaissance Dam, or GERD, on the Blue Nile. Tensions are already high between the nation and Egypt over how the water resources of the river will be distributed. A sudden change in climate, such as from a volcanic eruption, could make these "fraught hydropolitics even more fraught," Ludlow says.

"The 21st century has been lacking in explosive eruptions of the kind that can severely affect monsoon patterns. But that could change at any time," he says. "The potential for this needs to be taken into account in trying to agree on how the valuable waters of the Blue Nile are going to be managed between Ethiopia, Sudan and Egypt."

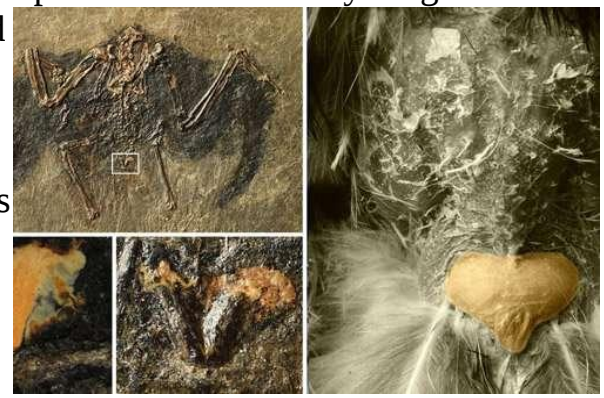
http://bit.ly/2yEV3Wz

Fatty bird gland preserved over 48 million years

48-million-year-old wax discovered in a bird fossil

October 18, 2017 by Bob Yirka report

Phys.org - A team of researchers from the U.S., Ireland, Germany and the U.K. has found evidence of preservation of a fatty oil gland from a 48-million-year-old fossilized bird. In their paper published in Proceedings of the Royal Society B, the group describes where the fossil was found, how it was tested and what their findings might mean for other fossilized bird remains.



A fossil preen gland in a 48-million-year-old bird, showing the fossil gland in detail as it was found before sampling and after preparation. The creamy white material is fossilised preen gland oil/wax. Right hand side: Modern bird with the preen gland prepared out from a modern Sickle-Billed Vanga (artificially coloured to highlight the preen gland). **University of Bristol**

Finding soft tissue preserved along with fossilized remains of long-dead creatures is extremely rare—tissue usually decomposes quite quickly, leaving modern scientists to make educated guesses about the nature of long-gone skin and organs.

But sometimes, conditions are just right for preservation of soft tissue, as the team working at the famed Messel Pit in Germany discovered when studying a fossilized bird. Upon examination of the remains, the team discovered an object near where its tail feathers had once been, which looked similar to the uropygial gland in modern birds—it produces an oil for feather preening. Preening with an oily material waterproofs feathers, and in some cases, can help birds ward off bacteria and fungi.

The team studied the object using pyrolysis gas chromatography-mass spectrometry to better understand its chemical composition and found that it was unlike those of the bird's other fossilized parts or the oily material in which the bird had been found. Instead, it very closely resembled the chemical makeup of modern uropygial glands.

Taken together, the team reports, all signs point to the object representing an example of soft tissue surviving over the course of millions of years.

The finding, the researchers also note, suggests that it might be possible that feathered flightless dinosaurs might have engaged in preening, as well. And they further note that it might be wise to take another look at other fossilized bird samples in museums to see if they have a preserved gland, as well.

The bird, which the team describes as approximately the size of a modern wren, appears to be of an unidentified species, possibly one belonging to the Messelirrisoridae family. It had a long beak and lived in a forest in what is now central Germany. The researchers suggest it probably spent its life among the trees rather than foraging on the ground.

More information: Shane O'Reilly et al. Preservation of uropygial gland lipids in a 48-million-year-old bird, Proceedings of the Royal Society B: Biological Sciences (2017). DOI: 10.1098/rspb.2017.1050

Abstract

Although various kinds of organic molecules are known to occur in fossils and rocks, most soft tissue preservation in animals is attributed to melanin or porphyrins. Lipids are particularly stable over time—as diagenetically altered 'geolipids' or as major molecular constituents of kerogen or fossil 'geopolymers'—and may be expected to be preserved in certain vertebrate tissues. Here we analysed lipid residues from the uropygial gland of an early Eocene bird using pyrolysis gas chromatography mass spectroscopy. We found a pattern of aliphatic molecules in the fossil gland that was distinct from the host oil shale sediment matrix and from feathers of the same fossil. The fossil gland contained abundant n-alkenes, n-alkanes and alkylbenzenes with chain lengths greater than 20, as well as functionalized long-chain aldehydes, ketones, alkylnitriles and alkylthiophenes that were not detected in host sediment or fossil feathers. By comparison with modern bird uropygial gland wax esters, we show that these molecular fossils are likely derived from endogenous wax ester fatty alcohols and fatty acids that survived initial decay and underwent early diagenetic geopolymerization. These data demonstrate the high fidelity preservation of the uropygial gland waxes and showcase the resilience of lipids over geologic time and their potential role in the exceptional preservation of lipid-rich tissues of macrofossils.

http://bit.ly/2xT6zJy

Three-quarters of the total insect population lost in protected nature reserves

Since 1989, in 63 nature reserves in Germany the total biomass of flying insects has decreased by more than 75 percent.

This decrease has long been suspected but has turned out to be more severe than previously thought. Ecologists from Radboud University together with German and English colleagues published these findings in the scientific journal PLoS ONE on October 18th.

In recent years, it became clear that the numbers of many types of insects such as butterflies and bees were declining in Western Europe and North America. 'However, the fact that flying insects are decreasing at such a high rate in such a large area is an even more alarming discovery,' states project leader at the Radboud University Hans de Kroon.

Thorough research

Entomologists (insect researchers) in Krefeld, Germany, led by Martin Sorg and Heinz Schwan, collected data over the past 27 years in 63 different places within nature reserves across Germany. Flying insects were trapped in malaise traps and the total biomass was then weighed and compared. The researchers from Nijmegen, Germany and England have now been able to analyse this treasure trove of data for the first time.

Decline also recorded in well-protected areas

The researchers discovered an average decline of 76 percent in the total insect mass. In the middle of summer, when insect numbers peak, the decline was even more severe at 82 percent. According to Caspar Hallmann from Radboud University who performed the statistical analyses, 'All these areas are protected and most of them are managed nature reserves. Yet, this dramatic decline has occurred.'

The exact causes of the decline are still unclear. Changes in the weather, landscape and plant variety in these areas are unable to explain this. The weather might explain many of the fluctuations within the season and between the years, but it doesn't explain the rapid downward trend.

A decline in other parts of the world too

Researchers can only speculate about the possible causes. 'The research areas are mostly small and enclosed by agricultural areas. These surrounding areas inflict flying insects and they cannot survive there. It is possible that these areas act as an 'ecological trap' and jeopardize the populations in the nature reserves,' explains Hallmann. It is likely that the results are representative for large parts of Europe and other parts of the world where nature reserves are enclosed by a mostly intensively used agricultural landscape.

Wake-up call

'As entire ecosystems are dependent on insects for food and as pollinators, it places the decline of insect eating birds and mammals in a new context,' states Hans de Kroon. 'We can barely imagine what would happen if this downward trend continues unabated.'

Because the causes of the decline are not yet known, it is difficult to take any concrete measures. The researchers hope that these findings will be seen as a wake-up call and prompt more research into the causes and support for long-term monitoring.

Measures

De Kroon: 'The only thing we can do right now is to maintain the utmost caution. We need to do less of the things that we know have a negative impact, such as the use of pesticides and prevent the disappearance of farmland borders full of flowers. But we also have to work hard at extending our nature reserves and decreasing the ratio of reserves that border agricultural areas.'

http://bit.ly/2l4Gp5G

How the Plague Outbreak in Madagascar Got So Bad, So Fast

The death toll from a recent plague outbreak in Madagascar is rising, according to news reports.

By Dyani Sabin, Live Science Contributor

The country's main agency responsible for tracking the disease, the Institut Pasteur de Madagascar (the Pasteur Institute of Madagascar), says the current outbreak, which began in August, has resulted in 805 cases of plague, causing at least 74 deaths, as of Oct. 16. (The latest report from the World Health Organization (WHO) from Oct. 12 places the death toll at 57 out of 684 cases.)

A council worker sprays disinfectant in a market in Antananarivo, the capital city of Madagascar. **Rijasolo/AFP/Getty**

Plague in Madagascar isn't new; the WHO estimates that, on average, there are about 400 cases of bubonic plague (the more common form of the disease) in the country annually. But the number of cases and

deaths in the current outbreak has exceeded health officials' estimates. So, what's different this year? And how can the outbreak be stopped?

One reason the plague that's spreading in Madagascar this year is so deadly is that the disease is spreading in its "pneumonic" form. Unlike the more common bubonic plague, which is spread from rats and fleas to humans, the pneumonic plague can spread from human to human, said Dr. Peter Small, an infectious-disease specialist and director of the Global Health Institute at Stony Brook University in New York.

Both forms of the plague are caused by the bacterium *Yersinia pestis*, which lives in fleas and rats. When the plague-causing bacteria get into a person's blood from a fleabite, it can travel to the lymph nodes. These lymph nodes become inflamed; in this form, they're called "buboes," which is how the bubonic plague gets its name. Along with inflamed lymph nodes, the plague causes symptoms similar to those of malaria or the flu, such as fever, chills and nausea.

The pneumonic plague develops when bubonic plague goes untreated and the infection moves from the lymph nodes into the lungs, Small told Live Science. Once in the lungs, the bacteria can be expelled into the air in suspended particles. There, it can live for more than a day, Small said. Madagascar is used to dealing with the bubonic form, which doesn't move human to human, said Small, so the high rate of pneumonic plague in this outbreak (about 65 percent of cases thus far) has made it particularly severe.

"If anyone has pneumonic plague, everyone else is at risk," Small said. Indeed, this airborne form of the plague can be deadly in as little as 24 hours after symptoms begin, said Lila Rahalison, a microbiologist who has studied the plague for 15 years.

Crowded conditions

Rahalison told Live Science that the current outbreak in Madagascar was also spurred by another factor: Patient zero — the first patient identified in the outbreak— fell ill while traveling toward the country's crowded capital city, Antananarivo. The patient, a 31-year-old man, started having malaria-like symptoms on Aug. 23, according to the WHO. Four days later, he started coughing and then died while traveling on a small, packed bus, WHO officials said. By the time the outbreak was detected, on Sept. 11, all of the people patient zero had infected had traveled to Antananarivo and beyond. Plague cases are now present in 35 of the 114 districts in Madagascar, according to the WHO.

The easy transmission of the disease and high population density in the capital led the disease to spread more quickly, Rahalison said. To slow the current outbreak, it's vital to control the spread of the plague and get lifesaving antibiotics to afflicted regions as fast as possible is vital, she said.

But these tasks can be challenging in a country like Madagascar, experts say. "For a health care system with [few] resources, it's hard to adapt to such a rapidly developing disease," said Dr. Simon Grandjean Lapierre, an infectious-disease specialist and medical microbiologist also at Stony Brook University. Pneumonic plague is fatal unless patients are treated with antibiotics, he added.

The government has shut down most of the country and stopped travel in an effort to contain the spread of the disease, Grandjean Lapierre told Live Science.

But in the Ranomafana National Park and Antananarivo, where Grandjean Lapierre conducts his research in Madagascar, most of the population doesn't seem very worried, possibly because the community hasn't internalized the increased dangers of the pneumonic plague versus the bubonic form, he said.

Moreover, "the Malagasy people are still shamed about the plague," said Rahalison, who is originally from Madagascar. "There is a stigma around it. For people, it's linked to the rats; rats are linked to dirt and poverty. So it's [a] difficult situation." Rahalison worries that this shame encourages sick people to hide — something she's encountered while working with the WHO in Madagascar.

"Now, we need a very fast response," Rahalison said. "It's critical that the outbreak be contained as soon as possible."

http://bit.ly/2yzQUDG

Petals produce a 'blue halo' that helps bees find flowers

Latest research has found that several common flower species have nanoscale ridges on the surface of their petals that meddle with light when viewed from certain angles.

These nanostructures scatter light particles in the blue to ultraviolet colour spectrum, generating a subtle effect that scientists have christened the 'blue halo'.

By manufacturing artificial surfaces that replicated 'blue halos', scientists were able to test the effect on pollinators, in this case foraging bumblebees. They found that bees can see the blue halo, and use it as a signal to locate flowers more efficiently.

Ursinia speciosa is a member of the Daisy family. The region at the base of the petals contains a dark pigment, but appears blue due to the presence of disordered floral nanostructures on the cell surface. **Edwige Moyroud**

While the ridges and grooves on a petal surface line up next to each other "like a packet of dry spaghetti", when analysing different flower species the researchers discovered these striations vary greatly in height, width and spacing - yet all produce a similar 'blue halo' effect.

In fact, even on a single petal these light-manipulating structures were found to be surprisingly irregular. This is a phenomenon physicists describe as 'disorder'.

The researchers conclude that these "messy" petal nanostructures likely evolved independently many times across flowering plant species, but reached the same luminous outcome that increases visibility to pollinators - an example of what's known as 'convergent evolution'. The study was conducted by a multidisciplinary team of scientists from the University of Cambridge's departments of plant sciences, chemistry and physics along with colleagues from the Royal Botanic Gardens Kew and the Adolphe Merkele Institute in Switzerland. The findings are published today in the journal Nature.

"We had always assumed that the disorder we saw in our petal surfaces was just an accidental by-product of life - that flowers couldn't do any better," said senior author Prof Beverley Glover, plant scientist and director of Cambridge's Botanic Garden.

"It came as a real surprise to discover that the disorder itself is what generates the important optical signal that allows bees to find the flowers more effectively."

"As a biologist, I sometimes find myself apologising to physicist colleagues for the disorder in living organisms - how generally messy their development and body structures can seem."

"However, the disorder we see in petal nanostructures appears to have been harnessed by evolution and ends up aiding floral communication with bees," Glover said.

All flowering plants belong to the 'angiosperm' lineage. Researchers analysed some of the earliest diverging plants from this group, and found no halo-producing petal ridges.

However, they found several examples of halo-producing petals among the two major flower groups (monocots and eudicots) that emerged during the Cretaceous period over 100 million years ago - coinciding with the early evolution of flower-visiting insects, in particular nectar-sucking bees.

"Our findings suggest the petal ridges that produce 'blue halos' evolved many times across different flower lineages, all converging on this optical signal for pollinators," said Glover.

Species which the team found to have halo-producing petals included Oenothera stricta (a type of Evening Primrose), Ursinia speciosa (a member of the Daisy family) and Hibiscus trionum (known as 'Flower-of-the-hour'). All the analysed flowers revealed significant levels of apparent 'disorder' in the dimensions and spacing of their petal nanostructures.

"The huge variety of petal anatomies, combined with the disordered nanostructures, would suggest that different flowers should have different optical properties," said Dr Silvia Vignolini, from Cambridge's Department of Chemistry, who led the study's physics team. "However, we observed that all these petal structures produce a similar visual effect in the blue-to-ultraviolet wavelength region of the spectrum - the blue halo."

Previous studies have shown that many species of bee have an innate preference for colours in the violet-blue range. However, plants do not always have the means to produce blue pigments. "Many flowers lack the genetic and biochemical capability to manipulate pigment chemistry in the blue to ultraviolet spectrum," said Vignolini. "The presence of these disordered photonic structures on their petals provides an alternative way to produce signals that attract insects."

The researchers artificially recreated 'blue halo' nanostructures and used them as surfaces for artificial flowers. In a "flight arena" in a Cambridge lab, they tested how bumblebees responded to surfaces with and without halos.

Their experiments showed that bees can perceive the difference, finding the surfaces with halos more quickly - even when both types of surfaces were coloured with the same black or yellow pigment.

Using rewarding sugar solution in one type of artificial flower, and bitter quinine solution in the other, the scientists found that bees could use the blue halo to learn which type of surface had the reward.

"Insect visual systems are different to human ones," explains Edwige Moyroud, from Cambridge's Department of Plant Sciences and the study's lead author. "Unlike us, bees have enhanced photoreceptor activity in the blue-UV parts of the spectrum." "Humans can identify some blue halos - those emanating from darkly pigmented flowers. For example the 'black' tulip cultivar, known as 'Queen of the night'."

"However, we can't distinguish between a yellow flower with a blue halo and one without - but our study found that bumblebees can," she said.

The team say the findings open up new opportunities for the development of surfaces that are highly visible to pollinators, as well as exploring just how living plants control the levels of disorder on their petal surfaces. "The developmental biology of these structures is a real mystery," added Glover.

http://bit.ly/2yJ5WXo

Turning brain cells into skin cells

Tel Aviv University and Weizmann Institute researchers transform mature cells from the brain, heart and more into skin cells

A new study published in Nature Communications reveals that it is possible to repurpose the function of different mature cells across the body -- and harvest new tissue and organs from these cells.

The research tracks the transformation of genetically manipulated cells into melanocytes, which are responsible for the production of skin pigment and essential to the body's auditory system.

The study, based on mouse models, was led jointly by Prof. Carmit Levy of the Department of Human Molecular Genetics and Biochemistry at Tel Aviv University's Sackler School of Medicine and Dr. Jacob Hanna of the Weizmann Institute of Science.

Reversing the irreversible

"When cells develop, they differentiate into different organs with varying functions: bone, intestine, brain, and so on," Prof. Levy says. "Our study proves, for the first time, that this process is not irreversible. We can turn back the clock and transform a mature cell that already plays a definite role in the body into a cell of a completely different kind.

"The applications of this are endless -- from transplants, which would eliminate long waiting lists and eliminate the common problem of immune system rejection of 'foreign' organs; to maybe one day curing deafness: taking any cell in the body and transforming it into melanocytes to aid in the restoration of hearing. The possibilities are really beyond the scope of the imagination," Prof. Levy continues.

The scientists took cells from different parts of the mouse -- stomach, intestine, connective tissue, heart and brain -- and placed these cells in a solution activating the genetic switch MITF (Microphthalmia-associated transcription factor), which is responsible for the production of melanocytes. Through this method, a stomach cell was turned into a skin cell.

"All of our genes are in all our cells, but genetic mechanisms allow them to manifest in the appropriate place while remaining dormant everywhere else," says Dr. Hanna. "Each cell has a kind of 'switch.' We activated the MITF switch to create melanocytes from cells designated for other purposes."

The generation of an entire genetically manipulated mouse is new and affords a scientific breakthrough that may save lives in the future, Prof. Levy concludes. "Future developments based on this method may enable the transformation of one tissue taken from the patient's own body into another tissue to replace the damaged organ, for example. Curing hearing loss is also a promising direction for this research because melanocytes are essential to our auditory system."

http://bit.ly/2iruXQE

Dutch courage -- Alcohol improves foreign language skills

Study shows that bilingual speakers' ability to speak a second language is improved after they have consumed a low dose of alcohol

A new study published in the Journal of Psychopharmacology, conducted by researchers from the University of Liverpool, Maastricht University and King's College London, shows that bilingual speakers' ability to speak a second language is improved after they have consumed a low dose of alcohol.

It is well-established that alcohol impairs cognitive and motor functions. 'Executive functions', which include the ability to remember, pay attention, and inhibit inappropriate behaviours, are particularly sensitive to the acute effects of alcohol.

Given that executive functions are important when speaking a second (non-native) language, one might expect that alcohol would impair the ability to speak a second language. On the other hand, alcohol increases self-confidence and reduces social anxiety, both of which might be expected to improve language ability when interacting with another person.

Furthermore, many bilingual speakers believe that it can improve their ability to speak a second language. The aim of this experimental study was to test these competing predictions for the first time.

Language performance

The researchers tested the effects of a low dose of alcohol on participants' self-rated and observer-rated ability to converse in Dutch. Participants were 50 native German speakers who were studying at a Dutch University (Maastricht) and had recently learned to speak, read and write in Dutch.

Participants were randomized to consume either a low dose of alcohol or a control beverage that contained no alcohol, before they chatted with an experimenter in Dutch for a few minutes. The exact dose of alcohol varied depending on participants' body weight, but it was equivalent to just under a pint (460ml) of 5% beer, for a 70kg male.

The chat was audio-recorded and participants' foreign language skills were subsequently rated by two native Dutch speakers who did not know if the participant had consumed alcohol or not (observer-ratings). Participants also rated their own Dutch language skills during the conversation (self-ratings).

The researchers found that participants who had consumed alcohol had significantly better observer-ratings for their Dutch language, specifically better pronunciation, compared to those who had not consumed alcohol. However, alcohol had no effect on self-ratings of Dutch language skills.

Implications and Limitations

Dr Inge Kersbergen, from the University of Liverpool's Institute of Psychology, Health and Society, who was involved in the study, said:

"Our study shows that acute alcohol consumption may have beneficial effects on the pronunciation of a foreign language in people who recently learned that language. This provides some support for the lay belief (among bilingual speakers) that a low dose of alcohol can improve their ability to speak a second language"

Dr Fritz Renner who was one of the researchers who conducted the study at Maastricht University, said: "It is important to point out that participants in this study consumed a low dose of alcohol. Higher levels of alcohol consumption might not have beneficial effects on the pronunciation of a foreign language."

Dr Jessica Werthmann who was one of the researchers who conducted the study at Maastricht University, said "We need to be cautious about the implications of these results until we know more about what causes the observed results. One possible mechanism could be the anxiety-reducing effect of alcohol. But more research is needed to test this."

The study was funded by Maastricht University, the Netherlands.

The full study, entitled 'Dutch courage? Effects of acute alcohol consumption on self-ratings and observer-ratings of foreign language skills', can be found here
http://journals.sagepub.com/doi/full/10.1177/0269881117735687

http://bit.ly/2yzULk8

Life in the city: Living near a forest keeps your amygdala healthier

MRI study analyzes stress-processing brain regions in older city dwellers

A study conducted at the Max Planck Institute for Human Development has investigated the relationship between the availability of nature near city dwellers' homes and their brain health. Its findings are relevant for urban planners among others.

Noise, pollution, and many people in a confined space: Life in a city can cause chronic stress. City dwellers are at a higher risk of psychiatric illnesses such as depression, anxiety disorders, and schizophrenia than country dwellers. Comparisons show higher activity levels in city dwellers' than in country dwellers' amygdala -- a central nucleus in the brain that plays an important role in stress processing and reactions to danger. Which factors can have a protective influence? A research team led by psychologist Simone Kühn has examined which effects nature near people's homes such as forest, urban green, or wasteland has on stress-processing brain regions such as the amygdala. "Research on brain plasticity supports the assumption that the environment can shape brain structure and function. That is why we are interested in the environmental conditions that may have positive effects on brain development. Studies of people in the countryside have already shown that living close to nature is good for their mental health and well-being. We therefore decided to examine city dwellers," explains first author Simone Kühn, who led the study at the Max Planck Institute for Human Development and now works at the University Medical Center Hamburg-Eppendorf (UKE).

Indeed, the researchers found a relationship between place of residence and brain health: those city dwellers living close to a forest were more likely to show indications of a physiologically healthy amygdala structure und were therefore presumably better able to cope with stress. This effect remained stable when differences in educational qualifications and income levels were controlled for. However, it was not possible to find an association between the examined brain regions and urban green, water, or wasteland. With these data, it is not possible to distinguish whether living close to a forest really has positive effects on the amygdala or whether people with a healthier amygdala might be more likely to select residential areas close to a forest. Based on present knowledge, however, the researchers regard the first explanation as more probable. Further longitudinal studies are necessary to accumulate evidence.

The participants in the present study are from the Berlin Aging Study II (BASE-II) - a larger longitudinal study examining the physical, psychological, and social conditions for healthy aging. In total, 341 adults aged 61 to 82 years took part in the present study. Apart from

carrying out memory and reasoning tests, the structure of stress-processing brain regions, especially the amygdala, was assessed using magnetic resonance imaging (MRI). In order to examine the influence of nature close to peoples' homes on these brain regions, the researchers combined the MRI data with geoinformation about the participants' places of residence. This information stemmed from the European Environment Agency's Urban Atlas, which provides an overview of urban land use in Europe.

"Our study investigates the connection between urban planning features and brain health for the first time," says co-author Ulman Lindenberger, Director of the Center for Lifespan Psychology at the Max Planck Institute for Human Development. By 2050, almost 70 percent of the world population is expected to be living in cities. These results could therefore be very important for urban planning. In the near future, however, the observed association between the brain and closeness to forests would need to be confirmed in further studies and other cities, stated Ulman Lindenberger.

Original publication

Kühn, S., Düzel, S., Eibich, P., Krekel, C., Wüstemann, H., Kolbe, J., Mårtensson, J., Goebel, J., Gallinat, J., Wagner, G. G., & Lindenberger, U. In search of features that constitute an "enriched environment" in humans: Associations between geographical properties and brain structure. Scientific Reports 7, Article number: 11920 (2017)

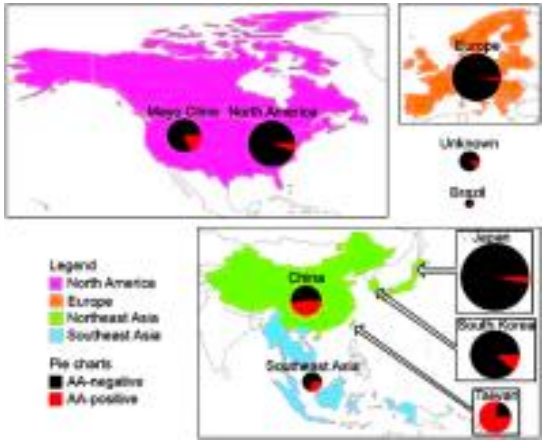
http://bit.ly/2z0ZTy0

Scientists reveal herbal remedies containing aristolochic acid may cause liver cancer

Scientists find that AA related mutations are common in Asian liver cancers, with Taiwan most intensely affected; Scientists call for greater public awareness of the dangers of AA in herbal products

Scientists from Singapore and Taiwan have revealed a decisive link between Aristolochic Acids (AA), a natural product of some plants used in herbal remedies, and liver cancers. Using mutational signature analysis, the researchers found that liver tumours had been exposed to AA, which had mutated many genes that cause cancer.

The team, led by Professor Steven Rozen from Duke-NUS Medical School (Duke-NUS), Professor Teh Bin Tean from the National Cancer Centre Singapore (NCCS), Professor Alex Chang from Johns Hopkins Medicine Singapore and Professor Hsieh Sen-Yung from Chang Gung Memorial Hospital in Taiwan, first sequenced the DNA of 98 liver cancers from Taiwan. Using mutational signature analysis, they found high numbers of AA-related mutations in over three-quarters of these cancers. Mutational signatures are patterns of changes in the DNA caused by mutagens, compounds that cause cancer.



Proportions of examined liver cancers with AA mutations in various regions.
Duke-NUS Medical School

"Although we knew that there was exposure to AA in Taiwan, we were very surprised to find such a high proportion of liver cancer sufferers had exposure to AA," said Professor Hsieh.

The team then looked at publicly available data on mutations from 1,400 liver cancers from around the world. While AA is found in plants used in traditional medicine worldwide, the team found high prevalence of exposure in other parts of East and Southeast Asia (see Fig. 1).

Professor Rozen noted: "This also was an unexpected finding. We did not suspect that exposure to AA was so prevalent in so many different areas."

AA, a known mutagen, was previously implicated in kidney and urinary tract cancers in Taiwan. In this new study, the researchers confirm that AA mutations are involved in causing liver cancer as well. "This was also another surprising finding of this study," added Professor Rozen.

Professor Teh from NCCS added, "This is a follow up study for our 2013 paper, when our team made a breakthrough in understanding the cancer-promoting action of AA in urinary tract cancer. Our new study establishes that AA is also implicated in liver cancer."

AA is a natural compound found in Aristolochia and Asarum plants. These plants are commonly used in traditional herbal remedies for many purposes including weight loss and slimming. AA has been officially banned in Europe since 2001 and in Singapore since 2004. Some herbs that contain AA have been banned in Taiwan since 2003, and in China, the use of some, but not all, AA-containing herbs in traditional medicine is restricted. While the United States Food and Drug Administration has issued warnings about herbs containing AA, their sale is unrestricted as long as they are labelled correctly and no health claims are made.

However, the effects of such bans may take years to materialise; so it could be years before rates of AA-associated cancers fall. In addition, herbs containing AA are easily available online. To complicate matters, herbs are often bundled and sold as formulations rather than individually, and some formulations might use herbs containing AA. Furthermore, herbs containing AA are sometimes improperly labelled, making it difficult for suppliers and consumers to be certain of the constituents of multi-herb formulations.

Plants that may contain AA include Asarum plants ((细辛, xì xīn), and powered xì xīn products manufactured in Taiwan and China were recalled in Singapore in 2014 because they contained AA. Other herbs that are likely to contain AA are: 马兜铃 (mǎ dōu líng), **青木香** (qīng mù xiāng). **天仙藤** (tiān xiān téng), **广防己** (guǎng fángjǐ), **关木通** (guān mù tōng), 寻骨风 (xún gǔ fēng), **朱砂**莲 (zhū shā lián, also written as **朱沙**莲).

As AA-containing plants and remedies are still widely available, Professor Alex Chang, noted that "public education and awareness are very important for avoiding exposure."

This study was published online on 18 October 2017, 14:00 US Eastern Time, in Science Translational Medicine, a publication with high scientific impact that focuses on practical medical advances. The research was supported by the Singapore Medical Research Council (NMRC/CIRG/1422/2015), the Singapore Ministry of Health via the Duke-NUS Signature Research Programmes, and the Chang Gung Medical Foundation in Taiwan.

http://bit.ly/2hXrkOA

Walking below minimum recommended levels linked to lower mortality risk

Investigators say walking has potential to significantly improve public's health

A new study concludes that walking has the potential to significantly improve the public's health. It finds regular walking, even if not meeting the minimum recommended levels, is associated with lower mortality compared to inactivity. The study appears early online in American Journal of Preventive Medicine.

Public health guidelines recommend adults engage in at least 150 minutes of moderate or 75 minutes of vigorous-intensity physical activity per week. But surveys show only half of U.S. adults meet this recommendation. Older adults are even less likely to meet minimum recommendations (42% ages 65-74 years and 28% ages 75 years and older).

Walking is the most common type of physical activity, and has been associated with lower risk of heart disease, diabetes, and breast and colon cancers. While several studies have linked overall moderate-vigorous physical activity to a reduced risk of death, relatively few have examined associations with walking specifically.

To learn more, investigators led by Alpa Patel, Ph.D., looked at data from nearly 140,000 participants in the Cancer Prevention Study II Nutrition Cohort. A small percentage (6-7%) in the study reported no moderate to vigorous intensity physical activity at baseline. Among the rest, about 95% reported some walking, and nearly half walked as their only form of moderate-vigorous physical activity.

After correcting for other risk factors, including smoking, obesity, and chronic conditions, the study found walking-only for less than 2 hours

per week was associated with lower all-cause mortality compared to no activity. Meeting 1 to 2 times the minimum recommendation (2.5-5 hours/week) through walking-only was associated with 20% lower mortality risk. Results for those exceeding recommendations through walking-only were similar to those who met recommendations.

Walking-only was most strongly associated with respiratory disease mortality, with approximately 35% lower risk comparing more than 6 hours/week of walking to the least active group. Walking-only was also associated with about 20% less risk of cardiovascular disease mortality and with about 9 percent less risk of cancer mortality.

"Walking has been described as the 'perfect exercise' because it is simple, free, convenient, doesn't require any special equipment or training, and can be done at any age," said Dr. Patel. "With the near doubling of adults aged 65 and older expected by 2030, clinicians should encourage patients to walk even if less than the recommended amount, especially as they age, for health and longevity."

Article: Patel AV, Hildebrand JS, Leach CR, et al. Walking in relation to mortality in a large prospective cohort of older U.S. adults. Am J Prev Med. 2017 [in press] DOI: 10.1016/j.amepre.2017.08.019.

http://bit.ly/2yGh6eK

Help sought from complementary and alternative medicine to remedy health problems

A new and extensive study has charted the use of complementary and alternative medicine in Europe.

A new and extensive study has charted the use of complementary and alternative medicine in Europe. It found that complementary and alternative medicine is being used in connection with various health problems, particularly in situations where help provided by conventional medicine is considered inadequate.

Headaches, back pain and other vexing conditions have made people turn to alternative forms of treatment. The study revealed that women and those with higher education use complementary and alternative medicine more often than others.

Research data were collected from more than 20 countries, with approximately 40,000 respondents participating in a study conducted in cooperation between the Universities of Helsinki, Tampere and Turku. Four treatment types were examined: traditional Asian treatments (Chinese medicine, acupuncture, acupressure), alternative medicine (homeopathy, herbal remedies), manual therapies (massage, chiropractic, osteopathy, reflexology), and mind-body therapies (hypnosis and spiritual healing).

Treatments used by one in four

According to the findings, one in four subjects in the study population had used complementary and alternative treatments in the past year. The most commonly used forms of treatment were massage (12%), homeopathy (6%), osteopathy (5%) and herbal remedies (5%). Most subjects had experienced only one treatment form.

"We also found that alternative and complementary medicine was used primarily in a complementary manner, or together with conventional medicine. This should be kept in mind both in practical patient care and public discourse, where these treatments are often framed as an alternative to conventional medicine," says Teemu Kemppainen, a researcher at the University of Helsinki.

Substantial differences between countries in treatment use

The prevalence of treatments varied greatly between the countries in the study. In Germany, nearly 40% of the study population had used complementary and alternative forms of treatment, whereas in Hungary the corresponding share was 10%. In Finland and Estonia, 35% of respondents had used these forms of treatment.

"The differences are partly explained by the fact that in some countries these treatments are covered by insurance. Some countries also train general practitioners in complementary medicine," notes Kemppainen.

The study concentrated on the use of complementary and alternative medicine in Europe. It was published in the Scandinavian Journal of Public Health. The study is based on European Social Survey data (Round 7), collected in 2014.

Publication (available in open access):

Kemppainen L, Kemppainen T, Reippainen J, Salmenniemi S & Vuolanto P (2017): Use of complementary and alternative medicine in Europe: Health-related and sociodemographic determinants. Scandinavian Journal of Public Health. Online before print, October 4, 2017 (https://doi.org/10.1177/1403494817733869)

http://bit.ly/2zse0sC

Itsy bitsy spider: Fear of spiders and snakes is deeply embedded in us

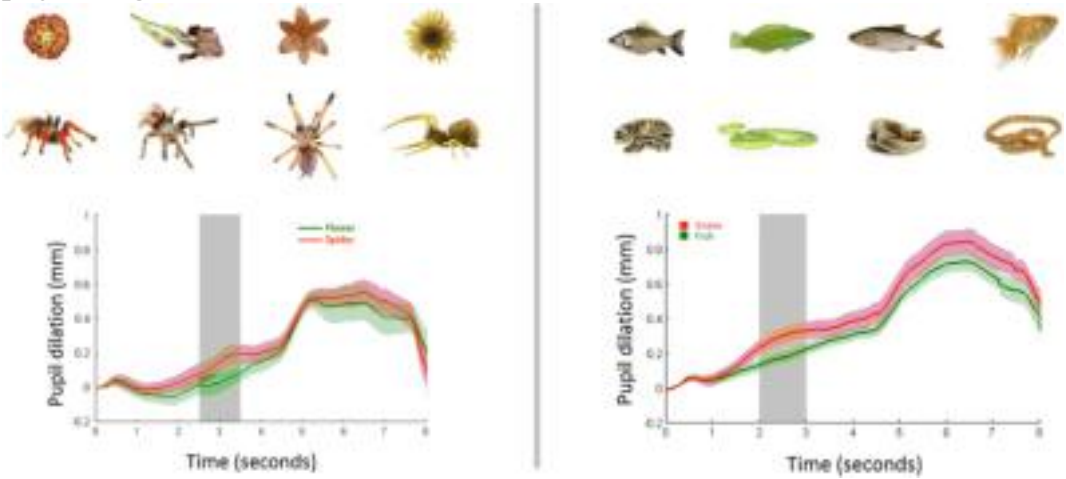
It has not been clear where the widespread aversion or anxiety to spiders or snakes originates

Presumably, in industrialized countries, especially in middle Europe, most people have never come across a poisonous spider or snake in the wild. In most of this countries there are nearly no spiders or snakes that pose a threat to humans. Nevertheless, there are few people that would not shiver at the thought of a spider crawling up their arm, however harmless it may be.

This fear can even develop into anxiety which limits a person's daily life. Such people are always on edge and cannot enter a room before it is declared "spider free" or cannot venture out into nature for sheer fear that they may encounter a snake. In developed countries one to five per cent of the population are affected by a real phobia of these creatures.

Until now, it was not clear where this widespread aversion or anxiety stems from. While some scientists assume that we learn this fear from our surroundings when we are a child, others suppose that it is innate.

The drawback of most previous studies on this topic was that they were conducted with adults or older children--making it hard to distinguish which behaviour was learnt and which was inborn. Such studies with children only tested whether they spot spiders and snakes faster than harmless animals or objects, not whether they show a direct physiological fear reaction.



When the babies saw a snake or a spider (second row) instead of a flower or a fish (first row) of the same size and colour, their pupils enlarged significantly (red versus green curve). This is a distinct signal that they felt stressed looking at these animals. **Max Planck Institute for Human Cognitive and Brain Sciences (MPI CBS)**

Scientists at the Max Planck Institute for Human Cognitive and Brain Sciences (MPI CBS) in Leipzig and the Uppsala University, Sweden, recently made a crucial observation: Even in infants a stress reaction is evoked when they see a spider or a snake. And this already at the age of six months, when they are still very immobile and have had little opportunity to learn that these animals can be dangerous.

"When we showed pictures of a snake or a spider to the babies instead of a flower or a fish of the same size and colour, they reacted with significantly bigger pupils", says Stefanie Hoehl, lead investigator of the underlying study and neuroscientist at MPI CBS and the University of Vienna. "In constant light conditions this change in size of the pupils is an important signal for the activation of the noradrenergic system in the brain, which is responsible for stress reactions. Accordingly, even the youngest babies seem to be stressed by these groups of animals."

"We conclude that fear of snakes and spiders is of evolutionary origin. Similar to primates, mechanisms in our brains enable us to identify objects as 'spider' or 'snake' and to react to them very fast. This obviously inherited stress reaction in turn predisposes us to learn these animals as dangerous or disgusting. When this accompanies further factors it can develop into a real fear or even phobia. "A strong panicky aversion exhibited by the parents or a genetic predisposition for a hyperactive amygdala, which is important for estimating hazards, can mean that increased attention towards these creatures becomes an anxiety disorder."

Interestingly, it is known from other studies that babies do not associate pictures of rhinos, bears or other theoretically dangerous animals with fear. "We assume that the reason for this particular reaction upon seeing spiders and snakes is due to the coexistence of these potentially dangerous animals with humans and their ancestors for more than 40 to 60 million years--and therefore much longer than with today's dangerous mammals. The reaction which is induced by animal groups feared from birth could have been embedded in the brain for an evolutionarily long time.

For modern risks such as knives, syringes or sockets, presumably the same is true. From an evolutionary perspective they have only existed for a short time, and there has been no time to establish reaction mechanisms in the brain from birth. "Parents know just how difficult it is to teach their children about everyday risks such as not poking their fingers into a socket", Hoehl adds with a smile.

http://bit.ly/2qYwOIV

World first: scientists find where HIV 'hides' to evade detection by the immune system

Discovering where infectious HIV 'hides' in the human body to evade detection by the immune system

In a decades-long game of hide and seek, scientists from Sydney's Westmead Institute for Medical Research have confirmed for the very first time the specific immune memory T-cells where infectious HIV 'hides' in the human body to evade detection by the immune system.

The team, led by Associate Professor Sarah Palmer from the University of Sydney, developed a pioneering full-length genetic sequencing assay for HIV. Using this test, the team found that genetically-intact HIV hides in specific subsets of CD4+ T-cells.

Associate Professor Palmer said that this next-generation test showed that HIV hides in the body's immune memory T-cells, which is how it avoids detection from the immune system.

"Previously it was thought that HIV was hiding primarily in central memory T-cells, but our new HIV genetic sequencing test has revealed that the majority of replication-competent virus is actually hiding in effector memory T-cells.

"HIV is really very clever. Essentially, it is hiding in the exact same cells within the immune system that are meant to attack it," she said.

Effector memory T-cells are the cells in the body that 'remember' previous infections and how to defeat them. These are the cells that provide life-long immunity to infections such as measles or chicken pox.

Associate Professor Palmer explained that only a very small proportion - approximately five per cent - of HIV is genetically intact. However, it is this small proportion of virus that hides in the effector memory T-cells and stops the immune system from fully destroying the virus and eliminating it from the body.

"When HIV replicates it makes a lot of errors and releases a lot of defective virus. "But this five per cent of genetically intact HIV is the key. This virus inserts its genome into the body's memory cells and sits there quietly avoiding detection by the immune system," Associate Professor Palmer explained.

"These infected cells go into a resting state and stop producing HIV, but these latent cells can wake up and start making infectious HIV.

"It is a ticking time bomb waiting to re-infect a patient. "The other 95 per cent of defective virus does send the immune system into

overdrive. We suspect that this 'junk' HIV can act as a decoy and draw attention away from the "real" virus hiding in the effector memory T-cells," she said.

Despite groundbreaking advances in the treatment of HIV, it remains a chronic illness across the globe. Neither a cure nor a vaccine has been achieved. "Current HIV drugs stop the virus from replicating, but there is still no way for us to 'cure' an individual with HIV. Patients need drugs or chemotherapy for the rest of their lives.

"This is a particular problem in the developing world where only 50 per cent of people have access to regular HIV therapies.

"If a person suddenly stops taking their HIV treatments, the virus hidden in effector memory T-cells would spring to life and start producing more HIV, and the virus will spread throughout the body within two weeks. "Now that we've identified where the replication-competent virus is hiding, we can start work towards targeting these cells with new therapies aimed at fully eliminating HIV from the body," Associate Professor Palmer concluded.

This curative research was conducted in conjunction with Drs. Frederick Hecht and Steven Deeks from the University of California, San Francisco. It is part of the Delaney AIDS Research Enterprise to Defeat HIV (DARE) and the research was funded by the NIH and the NHMRC.

This research was published today on the prestigious journal Cell Reports: http://www.cell.com/cell-reports/pdf/S2211-1247(17)31386-4.pdf

http://bit.ly/2yGTs0n

Dogs really can smell your fear, and then they get scared too

Dogs can smell your emotional state, and adopt your emotions as their own

By Jake Buehler

Dog owners swear that their furry best friend is in tune with their emotions. Now it seems this feeling of interspecies connection is real: dogs can smell your emotional state, and adopt your emotions as their own.

Science had already shown that dogs can see and hear the signs of human emotions, says Biagio D'Aniello of the University of Naples "Federico II", Italy. But nobody had studied whether dogs could pick up on olfactory cues from humans.

"The role of the olfactory system has been largely underestimated, maybe because our own species is more focused on the visual system," says D'Aniello. However, dogs' sense of smell is far superior to ours.

D'Aniello and his colleagues tested whether dogs could sniff out human emotions by smell alone. First, human volunteers watched videos designed to cause fear or happiness, or a neutral response, and the team collected samples of their sweat.

Next, the researchers presented these odour samples to domestic dogs, and monitored the dogs' behaviours and heart rates.

Dogs exposed to fear smells showed more signs of stress than those exposed to happy or neutral smells. They also had higher heart rates, and sought more reassurance from their owners and made less social contact with strangers.

We've always known that dogs collect information about their social partners through different sensory channels to decide how to respond to situations, says Márta Gácsi of Eötvös Loránd University in Budapest. "However, it is not easy to investigate such processes so that we can unfold the mechanisms and separate the channels," as this study has done, explains Gácsi.

Look at my face

D'Aniello's study suggests humans can inadvertently hijack their dogs' emotions by releasing smells. A second study suggests dogs can return the favour, using their expressive faces.

Juliane Kaminski of the University of Portsmouth, UK, and her colleagues have found that dogs' faces are most expressive when they know people are looking at them.

The researchers introduced dogs to a human who was either looking at them or facing away, and either presenting food or offering nothing.

The team analysed how much the dogs' facial movements varied in the four scenarios.

They found that the dogs' facial expressions varied the most when the person was looking at them. In contrast, Kaminski says there was no sign of a "dinner table effect", "which would predict that dogs try and look super-cute when they want something from the humans."

Puppy-dog eyes

"This adds to a growing body of evidence suggesting that dogs are very sensitive to human attention," says Kaminski.

It's not clear precisely how dogs visually signal us and how we respond, says Monique Udell of Oregon State University in Corvallis. "This kind of research is needed to fully understand the bidirectional nature of the human-dog relationship."

However, there is evidence that we are susceptible to these signals. Kaminski found that when dogs were being watched they often raised their eyebrows in a particular way. This eyebrow raise is known to give shelter dogs a better chance of being rehomed. It may make the dogs' eyes look "sad" or infant-like, creating an empathetic response.

It is not clear what role, if any, the domestication of dogs played in the development of these behaviours. It has been suggested that dogs' striking emotional intelligence towards humans is a product of the thousands of years we have spent with them.

Journal reference: Animal Cognition, DOI: 10.1007/s10071-017-1139-x
Scientific Reports, DOI: 10.1038/s41598-017-12781-x

http://bit.ly/2xYdUww

The end of pneumonia? New vaccine offers hope

Vaccine under development provides the 'most comprehensive coverage' to date and alleviates antimicrobial concerns, new study finds

BUFFALO, N.Y. -- In 2004, pneumonia killed more than 2 million children worldwide, according to the World Health Organization. By 2015, the number was less than 1 million.

Better access to antibiotics and improved nutrition account for part of the decline. But scientists say it's mostly due to vaccines introduced in the early 2000s that target up to 23 of the most deadly forms of the bacterium that causes pneumonia, Streptococcus pneumoniae.

Now, a new vaccine under development could deal another blow to the disease, lowering the number of deaths even further by targeting dozens of additional strains of S. pneumoniae, and anticipating future versions of the bacteria responsible for pneumococcal disease, which includes sepsis and meningitis.

The vaccine provoked an immune response to 72 forms of S. pneumoniae -- including the 23 mentioned above -- in lab tests on animals, according to new research published today (Oct. 20, 2017) in the journal Science Advances. The study represents the "most comprehensive" coverage of pneumococcal disease to date, researchers say.

"We've made tremendous progress fighting the spread of pneumonia, especially among children. But if we're ever going to rid ourselves of the disease, we need to create smarter and more cost-effective vaccines," says Blaine Pfeifer, PhD, associate professor of chemical and biological engineering at the University at Buffalo's School of Engineering and Applied Sciences, and the study's co-lead author.

The limitation of existing vaccines

Each strain of S. pneumoniae contains unique polysaccharides. Vaccines such as Prevnar 13 and Synflorix connect these sugars -- by the sharing of an electron -- to a protein called CRM197. The process, known as a covalent bond, creates a potent vaccine that prompts the body to find and destroy bacteria before they colonize the body.

While effective, creating covalent bonds for each strain of S. pneumoniae is time-consuming and expensive. Plus, this type of immunization, known as a conjugate vaccine, prompts the body to eliminate each of the targeted bacteria types -- regardless of whether the bacteria is idle or attacking the body.

Another vaccine, Pneumovax 23, contains sugars of 23 of the most common types of S. pneumoniae. However, the immune response it provokes is not as strong as Prevnar because the sugars are not covalently linked.

"Traditional vaccines completely remove bacteria from the body. But we now know that bacteria -- and in a larger sense, the microbiome -- are beneficial to maintaining good health," says Charles H. Jones, the study's other co-lead author. "What's really exciting is that we now have the ability -- with the vaccine we're developing -- to watch over bacteria and attack it only if it breaks away from the colony to cause an illness. That's important because if we leave the harmless bacteria in place, it prevents other harmful bacteria from filling that space."

Jones, who earned a PhD while working in Pfeifer's lab, has formed a company, Abcombi Biosciences, to bring the vaccine and other pharmaceutical products to market.

Co-authors of the study from UB's engineering school include Guojian Zhang, Roozbeh Nayerhoda, Marie Beitelshees (also of Abcombi), Andrew Hill (also of Abcombi) and Yi Li; Bruce A. Davidson and Paul Knight III, both faculty members from the Jacobs School of Medicine and Biomedical Sciences at UB; and Pooya Rostami of New York University's Langone Medical Center.

How the new vaccine works

Varieties of S. pneumoniae not covered by current immunizations are responsible for a small portion -- for example, 7 to 10 percent among U.S. children -- of pneumonia, meningitis and other cases of pneumococcal disease.

But officials worry that will change, as these less common forms -- and, potentially, yet-to-be discovered antimicrobial resistant strains -- replace the 23 more common types targeted by current immunizations.

According to results from the study, the new vaccine provokes a strong immune response (comparable to Prevnar) and is engineered in a way that makes it easy to add sugars (like Pneumovax) for a broad immune response.

Key to the technology is a liposome -- a tiny liquid-filled bubble made of fat -- that acts as a storage tank for the sugars. Because the sugars are not covalently bonded, it's possible that the liposome could host all of the sugars that identify individual strains of S. pneumoniae.

The research team added proteins at the surface of the liposome (also non-covalently) which, together with the sugars, provoke immunotherapy. According to tests performed on mice and rabbits, the new vaccine stimulated an immune response to 72 of the more than 90 known strains of S. pneumoniae. In many cases, it outperformed Prevnar and Pneumovax.

"The advantage of our approach is that we don't have to apply the more complex covalent chemistry that is required for Prevnar," Pfeifer says. "As a result, we can extend beyond the 13 types of sugars, potentially providing universal coverage against bacteria that cause pneumonia, meningitis, sepsis and other types of pneumococcal disease. It holds the promise of saving hundreds of thousands of lives each year."

The research was supported with funding from the National Institutes of Health and by the UB's Arthur A. Schomburg Fellowship Program.

http://bit.ly/2hWLbqH

'Selfish brain' wins out when competing with muscle power, study finds

Human brains are expensive - metabolically speaking. It takes lot of energy to run our sophisticated grey matter, and that comes at an evolutionary cost.

Now, a new investigation into the immediate trade-off that occurs inside us when we have to think fast and work hard at the same time is the first to demonstrate that - while both are impaired - our mental ability is less affected than our physical capacity.

Researchers say that the findings suggest a "preferential allocation of glucose to the brain", which they argue is likely to be an evolved trait - as prioritising quick thinking over fast moving, for example, may have helped our species survive and thrive.

Scientists from the University of Cambridge's PAVE (Phenotypic Adaptability, Variation and Evolution) research group tested 62 male students drawn from the University's elite rowing crews. The participants had an average age of 21.

The rowers performed two separate tasks: one memory, a three minute word recall test, and one physical, a three minute power test on a rowing machine.

They then performed both tasks at once, with individual scores compared to those from previous tests. As expected, the challenge of rowing and remembering at the same time reduced both physical and mental performance. However, the research team found that change in recall was significantly less than the change in power output.

During the simultaneous challenge, recall fell by an average of 9.7%, while power fell by an average of 12.6%. Across all participants the drop in physical power was on average 29.8% greater than drop in cognitive function.

The team say the results of their new study, published today in the journal Scientific Reports, add evidence to the 'selfish brain' hypothesis: that the brain has evolved to prioritise its own energy needs over those of peripheral organs, such as skeletal muscle.

"A well-fuelled brain may have offered us better survival odds than well-fuelled muscles when facing an environmental challenge," said Dr Danny Longman, the study's lead author from the PAVE team in Cambridge's Department of Archaeology.

"The development of an enlarged and elaborated brain is considered a defining characteristic of human evolution, but one that has come as a result of trade-offs. "At the evolutionary level, our brains have arguably cost us decreased investment in muscle as well as a shrunken digestive system. "Developmentally, human babies have more stored fat than other mammals, acting as an energy buffer that feeds our high cerebral requirements.

"On an acute level, we have now demonstrated that when humans simultaneously experience extremes of physical and mental exertion, our internal trade-off preserves cognitive function as the body's priority."

The adult brain derives its energy almost exclusively from the metabolism of glucose. Yet skeletal muscle mass is also energetically expensive tissue, accounting for 20% of the human male 'basal metabolic rate' - the energy used when doing nothing.

Longman says a limited supply of blood glucose and oxygen means that, when active, skeletal muscle becomes a "powerful competitor" to the brain. "This is the potential mechanism for the fast-acting trade-off in brain and muscle function we see in just a three minute window."

"Trade-offs between organs and tissues allow many organisms to endure conditions of energy deficit through internal prioritising. However, this comes at a cost," said Longman.

He points to examples of this trade-off in humans benefiting the brain. "The selfish nature of the brain has been observed in the unique preservation of brain mass as bodies waste away in people suffering from long-term malnutrition or starvation, as well as in children born with growth restriction."

Notes to editors: The study:

***Protocol A** - isolated power test:*

Participants rowed at maximal effort for 3 minutes, and their average Wattage was recorded.

***Protocol B** - isolated recall test:*

Participants performed a free recall word task in which they were shown 75 words from the Toronto Word Pool for a 3 minute period. They then had 5 minutes to recall and write as many words as possible. The number of words correctly recalled during a given time period was recorded.

***Protocol C** - combined 'trade-off' test:*

Participants did both (but with a different word set), and their average Wattage and number of words correctly recalled was recorded. Researchers used 'paired samples t-tests' to compare power output between Protocols A and C, and for comparing free recall in Protocols B and C. They then compared the two differences, and found that the percentage change in free recall was significantly less than the percentage change in power output - an average of 29.8%.

http://bit.ly/2xWCD4c

A universal food and alarm cue found in mammalian blood

Ancient food and alarm molecule within blood odour signals blood

Predators use the smell to home in on wounded animals, whereas mammalian prey species avoid the same odour. This suggests that there may be an old, preserved, evolutionarily food and alarm molecule within the blood odour mixture that is the signal of blood. Researchers from Radboud University report in Scientific Reports of 20 October that they may have found this molecule called E2D, and it seems to affect humans as well.

Like most naturally occurring odours that are important to animals, the odour of blood is composed of a mixture of hundreds of different odour molecules. However, unlike other 'chemosignals' that vary between species, the odour of blood seems to be universally important to animals. Now researchers may have found an old, preserved, food and alarm molecule within the blood odour mixture that is the signal of blood. "It's really special, and it smells kind of metallic," says Artin Arshamian from Radboud University (research group Culture, Meaning and Cognition) and the Karolinska Institutet in Sweden.

E2D molecule

Arshamian explains, "The name of this cue is trans-4,5-epoxy-(E)-2-decenal, a single molecule that was isolated from pig blood by our collaborator Matthias Laska from Linköping University in Sweden. In the lab, it goes by the more easily pronounced E2D." To assess behavioural responses to E2D across taxonomically distant species, the researchers worked with scientists across many disciplines and countries.

Humans and other animals

The study tested humans, wolves, mice and blood-sucking flies. The researches first showed that blood-sucking stable flies liked E2D as much as the odour of real blood. Next, they showed that when wolves smelled it on a scented log they reacted to it as if it were the real deal: licking, biting and guarding it as if it were freshly killed prey. When they tested the smell of E2D in the prey species mice, the reactions were the same as the strong avoidance reactions induced by the full blood odour.

The researchers next extended their experiments to include humans. Here they showed that when humans smelled the E2D, they exhibited an automatic avoidance response initiated by a backward-leaning motion. They also started sweating more. However, this was not because participants thought the odour was unpleasant. In a follow-up experiment, the researchers also showed that E2D increased visual vigilance and attention. When smelling E2D, participants detected emotional visual stimuli more quickly.

One cue, two functions

Arshamian continues, "This finding is unique, as it is the first demonstration of a single chemical cue with the dual function of informing both approach and avoidance in a predator-prey predicted manner across taxonomically distant species. Importantly, it is the first known chemosignal that affects human and non-human animals alike. In humans, the effect of E2D went beyond simple peripheral responses by modulating more complex cognitive functions prototypical for a defensive system."

Shed light on human evolution

The omnipresent adaptation to E2D indicates that the selection pressure for this chemical cue is preserved through evolution. This can shed light on human evolution, our formation as a species. "Our finding in humans fits in with the paleontological data showing that early primates were small-bodied insectivores. There is no question that humans are opportunistic predators, but we probably evolved from a prey species and some aspects of this trait lingers on," says principal investigator Johan Lundström, associate professor at the Karolinska Institutet in Sweden.

More information: Artin Arshamian et al. A mammalian blood odor component serves as an approach-avoidance cue across phylum border - from flies to humans, Scientific Reports (2017). DOI: 10.1038/s41598-017-13361-9

http://bit.ly/2qF3CK9

Key discoveries offer significant hope of reversing antibiotic resistance

Resistance to antibiotics is becoming increasingly prevalent and threatens to undermine healthcare systems across the globe.

Antibiotics including penicillins, cephalosporins and carbapenems are known as β-lactams and are the most commonly prescribed worldwide.

In the first paper, University of Bristol researchers defined the relative importance of two mechanisms associated with β-lactam antibiotic resistance. In one, bacteria restrict the entry of antibiotics into the cell; in the other, bacteria produce an enzyme (a β-lactamase), which destroys any antibiotic that gets into the cell. The latter was found to be the more important of the two mechanisms. These findings imply that if chemicals could be developed to inhibit β-lactamase enzymes, a significant proportion of antibiotic resistance could successfully be reversed.

Building on these findings, and working in partnership with chemists at the University of Oxford and the University of Leeds, in the second paper, Bristol researchers studied the effectiveness of two types of β-lactamase enzyme inhibitor in a bacterium known to be highly resistant to common antibiotics.*

Using a variety of approaches, the authors studied avibactam, an inhibitor that has recently been introduced into clinical practice, and a "bicyclic boronate" inhibitor, which was first reported by the Oxford/Leeds/Bristol team in 2016.

They found both inhibitors failed to consistently protect the β-lactam antibiotic, ceftazidime, from attack by the β-lactamase enzyme. However, when paired with a different β-lactam antibiotic =, aztreonam, the inhibitors worked extremely well and killed some of the most resistant bacteria ever seen in the clinic.**

Dr Matthew Avison, Reader in Molecular Bacteriology from the University of Bristol's School of Cellular & Molecular Medicine, and senior author for both studies said:

"Our bacteriology research has further demonstrated that β-lactamases are the real "Achilles heel" of antibiotic resistance in bacteria that kill thousands of people in the UK every year.

"Structural/mechanistic work on β-lactamase enzymes, including that led by my colleague Dr Jim Spencer, is helping to drive the discovery of wave after wave of β-lactamase inhibitors, including the potentially game-changing bicyclic boronate class, shown to be effective in our research, and recently successful in phase one clinical trials.

"Two β-lactamase inhibitors have recently been licenced for clinical use: avibactam and vaborbactam. Our work shows that avibactam might more successfully be deployed with aztreonam instead of ceftazidime as its antibiotic partner. We are delighted to see that this combination has entered clinical trials, and has recently saved the life of a patient in the USA who was suffering from a previously untreatable infection."

"This is an exciting time for researchers studying β-lactamase inhibitors. At the risk of sounding like King Canute, it is the first time for a decade that there is some genuine positivity about our ability to turn back the rising tide of β-lactam antibiotic resistance."

**The World Health Organisation recently placed cephalosporin and carbapenem resistant Gram-negative bacteria of the Enterobacteriaceae and Non-Fermenter groups at the top of its Priority List of Pathogens where Research and Development of novel treatment strategies is needed. The first paper investigated cephalosporin and carbapenem resistance in Klebsiella pneumoniae, one of the most clinically important members of the Enterobacteriaceae group.*

***In the second paper, researchers studied the abilities of two β-lactamase inhibitors to reverse cephalosporin and carbapenem resistance in a member of the Non-Fermenter group, Stenotrophomonas maltophilia. This bacterium causes severe infections in immunocompromised patients and is usually resistant to all β-lactam antibiotics because it produces two β-lactamase enzymes.*

The papers discussed are:

Paper 1:*Jiménez-Castellanos JC, Wan Nur Ismah WAK, Takebayashi, Y, Findlay, J., Schneiders T, Heesom KJ, Avison MB. Envelope proteome changes driven by RamA overproduction in Klebsiella pneumoniae that enhance acquired β-lactam resistance. Journal of Antimicrobial Chemotherapy 2017 doi10.1093/jac/dkx345. [Epub ahead of print]*

Paper 2:*Calvopiña K, Hinchliffe P, Brem J, Heesom KJ, Johnson S, Cain R, Lohans CT, Fishwick CWG, Schofield CJ, Spencer J, Avison MB. Structural/mechanistic insights into the efficacy of nonclassical β-lactamase inhibitors against extensively drug resistant*

Stenotrophomonas maltophilia clinical isolates. Molecular Microbiology 2017 doi: 10.1111/mmi.13831. [Epub ahead of print].

http://bit.ly/2yJHBAu

Evolution experiment has now followed 68,000 generations of bacteria

It's basically a time machine. For bacteria.

Diana Gitig - 10/22/2017, 10:00 PM

On February 24, 1988, Richard Lenski seeded 12 flasks with E. coli and set them up to shake overnight at 37ºC. But he seeded them with only enough nutrients to grow until early the next morning. Every single afternoon since then, he (or someone in his lab) has taken 100 microliters of each bacterial solution, put them into a new flask with fresh growth media, and put the new flask in the shaker overnight. Every 75 days—about 500 bacterial generations—some of the culture goes into the freezer.

The starvation conditions are a strong pressure for evolution. And the experiment includes its own time machine to track that evolution.

The pivotal piece of technology enabling this experiment is the -80ºC freezer. It acts essentially, Lenski says, as a time machine. The freezer holds the bacterial cultures in a state of suspended animation; when they are thawed, they are completely viable and their fitness can be compared to that of their more highly evolved descendants shaking in their flasks. As an analogy, imagine if we could challenge a hominin from 50,000 years ago to a hackathon. (Which she would probably win, because the paleo diet.)

So cool, right? The MacArthur Foundation thought so, too—it gave Lenski a grant in 1996, all the way back at around generation 17,000 or so. The experiment is now at generation 68,113 (approximately).

The bacteria have been maintained in the same medium—the same environment—over the course of the experiment. Their food source is glucose, which is calibrated to wane over the 24 hours before the passage to the next flask. This diminishing food supply is the only selective pressure the bacteria experience.

The competitive fitness of all 12 cultures has improved over time; the cells are bigger than they were at the start of the experiment, they utilize glucose more efficiently, and they grow faster. The rate of improvement has declined over the course of the experiment, but the rate at which genetic mutations accrue does not.

The 12 populations tend to get mutations in the same set of genes, but they don't get the same mutations within those genes; they are each finding their own path toward the same goal of optimal fitness, much like climbers each find their own paths to the same peak. And although the rate of mutation has slowed, it has not ceased. So Lenski concludes that—even in their simple, relatively static environment, and even after 68,113 generations—there are still molecular tweaks the bacteria can make to become fitter.

At about 20,000 generations, one of the 12 cultures evolved the ability to survive by eating citrate in addition to glucose. It has remained the only one of the 12 to have developed this ability and, over time, it became less able to deal with glucose as an energy source. Since the inability to metabolize citrate is kind of a hallmark of E.coli, are these guys even E. coli anymore? Or a new species?

It is not only the fitness of current bacteria that can be compared to their ancient unfrozen forbears. Lenski sequenced the genomes of each frozen culture so he can disentangle the dynamics of evolution at the molecular level.

Six of the 12 initial populations have become hypermutators. They picked up early mutations in genes controlling DNA repair, which then enabled them to accrue more mutations in the rest of their genomes. These bacteria undergo bouts of molecular evolution that yield jumps in their degree of genetic diversity. The other six populations are nonmutators; these guys accumulate mutations at a much more stately pace. The strain that eats citrate started as a nonmutator, but once it gained the ability to exploit a new food source, it began to mutate more rapidly to refine its new ability.

The length of time that each mutation sticks around sheds light on the selective forces at play. It does not seem to be the case that one beneficial mutation arises at a time and sweeps through a population. Rather, a few occur in rapid succession, and these compete for dominance. But one doesn't always win; in most populations, the mutations segregate into groups, creating different subcultures within each flask. These subcultures have a tenuous coexistence, with their relative abundance shifting over time.

Random, stochastic mutations allow species to diversify. But selective pressures push them toward sameness, by forcing them to thrive under limiting conditions. The 60,000 generations of E. coli already in Richard Lenski's freezer have started to show how these opposing forces shape evolution; who knows what the next 60,000 will reveal?

Nature, 2017. DOI: 10.1038/nature24287 (About DOIs).

http://bit.ly/2zHxsT8

Fermi's Paradox finished? Perhaps ET is abundant and we just can't see it

NASA's Pluto chief suggests aliens may thrive in subsurface oceans – but be blind to the universe.

Richard A Lovett reports.

Alan Stern, principal investigator for NASA's New Horizons mission to Pluto, and a planetary scientist at the Southwest Research Institute in Boulder, Colorado, has a new answer for one of the oldest conundrums in astrobiology. If alien civilizations exist, why can't we find them?

It's a puzzle known as the Fermi Paradox, and Stern's answer is an unusual one. Perhaps, he said this week at a meeting of the American Astronomical Society's Division for Planetary Sciences in Provo, Utah, aliens exist, but are trapped in subsurface oceans on cold worlds such as Saturn's moon Enceladus or Jupiter's moon Europa.

The Fermi Paradox was first propounded by Nobel laureate physicist Enrico Fermi, who famously wondered why, if alien civilizations are out there, we haven't had unambiguous contact with them. It's a conundrum that's done nothing but intensify since Fermi first propounded it in the 1950s, as radio astronomers have vainly scoured the skies seeking to intercept alien transmissions similar to those our own planet has been producing for the better part of a century.

Perhaps we really are alone, unique in the universe. Or perhaps something, ranging from differences in technology to Borg-like marauders that home in on advanced civilizations and destroy them the moment they reveal their presence, is keeping us from spotting them. Perhaps habitable planets capable of developing life are simply so rare that we have yet to point our radio telescopes in the right direction.

Stern's idea is simpler. Perhaps, he says, most worlds capable of sustaining life aren't like Earth, with its continents, surface water, and atmosphere. Maybe they are icy bodies with thick "lids" enclosing interior oceans.

Until recently we didn't even know such worlds existed. But now, we know they are quite common, at least in our own solar system. Ours has only one Earth, but it may eventually prove to have dozens of Europas.

Alien civilizations living on these worlds, Stern says, might never come into contact with anyone else. Partly that's because the thick crusts covering them would block us from ever hearing their internal transmissions.

But such civilizations might not even know there was anything interesting above their own "roof." And if they were motivated to drill through it to reach the unknown, they might not even know what those lights in the sky mean – assuming they have eyes able to see them.

And if they were nonetheless disposed toward space travel, they would have to carry large volumes of water, rather than air, for life support. That's a huge impediment, Stern says, because "everything we know about space travel involves making the spacecraft lighter."

Yet another factor, he says, is that "exterior" ocean worlds like Earth are "shooting galleries" for bad things descending from space. "We all

know about impacts like those that very likely terminated the Cretaceous Period and the dinosaurs," he says. "But there are many other dangers. This doesn't apply to interior oceans."

Such planetsl, he adds, don't even have to be in the traditional habitable zone close to their suns, or even anywhere close to it. "An ocean inside of Pluto is just as wet and just as warm as an ocean in the interior of a Galilean moon," he says.

The response from others has been mixed. Award-winning science fiction writer and space scientist David Brin agrees that Stern is correct in pointing out that the vast majority of ocean worlds are likely to be ice-covered. "And Alan is right that few or none would ever get free of their roof," he says.

But that has no bearing on the Fermi Paradox, he adds, because all that Stern has done is to vastly multiply the number of worlds that might develop intelligent life, without explaining why none of the other "roofless" ones like Earth have so far revealed themselves.

NASA astrobiologist Chris McKay agrees. "We already know enough about exoplanets to say that even if earthlike worlds are not the dominant habitable world in the galaxy, there should still be gazillions of earthlike worlds out there. The Fermi Paradox still holds for that set," he says.

Nor is it clear that lidded ocean worlds will be suitable for the origin of any life, let alone intelligent life. To begin with, McKay says, there is serious debate over whether life can develop in an ocean, where currents can disperse and dilute its chemical precursors. Many biologists believe it needs surface ponds that periodically dry out, thereby concentrating the available chemicals to critical levels.

But even if life can develop in an interior ocean world, there's another problem. "It is generally thought multicellular life requires high oxygen levels," he says. "There is no evidence for this in the plume of Enceladus, [and] the presence of hydrogen and methane would suggest its strong absence."

Paul Davies, director of the BEYOND Center for Fundamental Concepts in Science at Arizona State University, Tempe, however, is more sanguine. In his 2010 book *The Eerie Silence*, he too examined the prospect of life on "lidded" ocean worlds such as Europa, noting that there is a difference between what it takes for life to reach intelligence and what is needed for an alien race to develop science and technology.

"So many cultural factors contributed to what we call 'the scientific method' that even if intelligence is common, scientific inquiry may not be," he tells Cosmos.

One of these might well be the ability to see the stars. "Astronomy was the midwife of human science," he says. "If you can't see the sky or develop a belief in gods or an intelligible cosmic order, why on Europa would you ever think of science?"

Stern, on the other hand, notes that his paper is simply the starting point for continued discussion. "We are at the beginning of understanding," he says. "Fasten your seat belt."

http://bit.ly/2zudqmH

Biosimilar drugs could cut US health spending by $54 billion over next decade

But regulatory rules still key to achieving future savings

Introducing "biosimilar" versions of complex biologic drugs used to treat illnesses such as cancer and rheumatoid arthritis could cut health care spending in the United States by $54 billion over the next decade, according to new analysis from the RAND Corporation.

The savings estimate is about 20 percent larger than a similar analysis done by RAND researchers three years ago, representing both improved analysis methods and rapid growth in spending for biologics overall.

"Biologics account for the fastest-growing segment of prescription drug spending, but biosimilars have the potential to help slow some of the increase," said Andrew Mulcahy, lead author of the study and a policy researcher at RAND, a nonprofit research organization.

"However, there remains many important industry, regulatory and policy decisions to be made that will influence whether such savings are realized."

Biologics are complex, protein-based drugs manufactured in living systems and include insulin, monoclonal antibodies to block inflammation in rheumatoid arthritis, and a range of drugs to treat cancer, multiple sclerosis and other serious diseases.

While biologics are important treatments for many conditions, they often are expensive and patient copays for the treatments can be several thousand dollars per year. While 1 percent to 2 percent of the nation's population is treated with a biologic each year, the drugs accounted for 38 percent of prescription drug spending in 2015. In addition, biologics accounted for 70 percent of the growth in prescription drug spending in the U.S. between 2010 and 2015.

Biosimilars are very similar to already approved "reference" biologics in terms of potency, safety and efficacy, but manufactured by different companies. Biosimilars can be approved for marketing by the federal Food and Drug Administration after the manufacturer of the reference biologic enjoys several years of patent and exclusivity protection.

The Biologics Price Competition and Innovation Act, enacted as part of the 2010 Patient Protection and Affordable Care Act, authorized the FDA to create a new approval pathway for biosimilars with the goal of promoting competition. This new pathway is faster and less costly for biosimilar developers.

RAND researchers developed their estimate of savings from biosimilars by examining other studies that have examined the issue, reviewing the sales history of more than 100 biologic drugs and examining the brief experience of the one biosimilar drug that has been marketed in the U.S.

RAND researchers estimate that that biosimilars will cut spending on biologics by about 3 percent over the next decade. The range of the new savings estimate given reasonable ranges of key assumptions -- like the price of biosimilars versus reference biologics and biosimilar market share -- varied from $24 billion to $150 billion from 2018 through 2027.

While expected to produce less-dramatic savings than an earlier generation of less-complex generic drugs, the introduction of biosimilars into the U.S. marketplace is expected to increase competition and drive down prices, resulting in savings for patients, health care payers and taxpayers. Lower costs also could improve access to biologic drugs, which could lead to higher spending overall unless the treatments helped lower hospitalizations or other costs.

"The actual savings hinge on the evolving competitive landscape in the pharmaceutical industry, regulatory decisions, and insurer efforts to promote biosimilar uptake through payment rates and other strategies," Mulcahy said. "Future research will be needed as more biosimilars come to market to see whether savings are realized and who benefits from any reductions in spending."

Support for the research was provided by Sandoz Inc., a Novartis company.

The perspective, "Biosimilar Cost Savings in the U.S.: Initial Experience and Future Potential," is available at http://www.rand.org. Other authors of the study are Jakub P. Hlávka and Spencer Case.