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# Red Meat OK'd in New Guideline But Critics Call Foul

***Consuming red and processed meat at current levels is safe according to guidelines published online***

Consuming red and processed meat at current levels is safe according to guidelines published online today in *Annals of Internal Medicine*, the American College of Physician's flagship journal. The NutriRECS guideline is based on four systematic reviews that considered various data sources and health outcomes, including overall mortality, cardiac health, and cancer. But critics are already up in arms.

A spokesperson for the American Cancer Society (ACS) likens the new advice to saying it's safe to ride a bike without a helmet, despite clear evidence of the risk.

"It is important to recognize that this group reviewed the evidence and found the same risk from red and processed meat as have other experts," said Marji McCullough, ScD, RD, senior scientific director, epidemiology research, with the ACS, in a statement. "So they're not saying meat is less risky; they're saying the risk that everyone agrees on is acceptable for individuals."

The new dietary guideline, developed by a 14-member international consortium, suggests most adults can continue their current levels of unprocessed red meat and processed meat consumption with little risk to their long-term health. The conclusion runs counter to established US guidelines that recommend just one weekly serving of red and processed meat.

The consortium weighed the data from the health-related systematic reviews as well as one that assessed health-related values and preferences around meat consumption.

"On the basis of these, we made a weak recommendation that most people need not reduce their red meat and processed meat consumption," lead guideline author Bradley C. Johnston, PhD, an associate professor of epidemiology and community health at Dalhousie University in Halifax, Nova Scotia, told *Medscape Medical News.* "We cannot say with any certainty that eating red meat or processed meat causes cancer, diabetes, or heart disease."

The systematic reviews of harms approached meat consumption from the following perspectives: low-vs-high intake and cardiometabolic/cancer outcomes; consumption and all-cause mortality and cardiometabolic outcomes; reduced intake and cancer incidence and mortality; and intake patterns and cardiometabolic and cancer outcomes.

Among 12 randomized controlled trials, the panel found no statistically significant or important association between decreasing intake by three servings per week and a reduction in cancer, diabetes, or heart disease. In addition, in cancer, for example, a review of approximately 180 cohort studies with millions of participants found a reduced risk of cancer ranging from 0.1% to 1.3% (1 to 13 fewer cases per 1000 people over a lifetime).

"The problem is, with low-quality evidence, there is considerable uncertainty as to whether the risk reduction is attributable (to) red meat or other factors, such as higher smoking or alcohol consumption, lower socioeconomic status, or possibly adverse genetic factors," Johnston said.

A related review of 54 studies involving more than 63,000 individuals in English-speaking countries assessed health values and preferences identified two main themes: reasons for meat consumption and willingness to reduce intake to avoid adverse health effects.

According to Claudia Valli, MSc, of the Iberoamerican Cochrane Centre in Barcelona, Spain, and colleagues, people who choose to eat meat enjoy doing so and may be reluctant to change their intake. "Our results highlight the inappropriateness of assuming that informed persons would choose to reduce meat consumption on the

basis of small and distant health benefits, particularly if the benefits are uncertain," they write.

**Faulty Methodology?**

In stark disagreement with the panel's conclusions, the Harvard T.H. Chan School of Public Health in Boston, Massachusetts, issued a statement calling the consortium's recommendations "irresponsible" and faulting its evaluative methodology.

"The GRADE criteria used by the authors were mainly developed for evaluating evidence from drug trials," said Edward Giovannucci, MD, ScD, a professor of nutrition and epidemiology at Harvard Medical School. "For dietary, lifestyle, and environmental factors, modified grading systems have been developed, such as hierarchies of evidence applied to lifestyle medicine," he told *Medscape Medical News.*

When asked about this, Johnston countered that the National Academies of Sciences, Engineering, and Medicine as well as 110 organizations recommend GRADE for dietary intakes.

Giovannucci's criticism doesn't stop at methodology.

He notes, as ACS does, that some prospective cohorts do show an association between moderate reduction in red and processed meat consumption and lower total mortality (13%), cardiovascular disease mortality (14%), cancer mortality (11%), and type 2 diabetes risk (24%). "Based on these data and the prevalence of meat consumption according to National Health and Nutrition Examination Survey data, one can estimate that a moderate reduction in red meat consumption could hypothetically reduce mortality by 7.6% or approximately 200,000 US deaths per year," he said.

Furthermore, the analyses failed to consider randomized controlled studies of red meat in relation to cardiovascular risk factors. These show that red meat increases blood levels of LDL cholesterol and triglycerides, which consistently predict higher risk of cardiovascular disease.

An accompanying editorial notes that Valli's review on values reveals nonhealth reasons for limiting meat consumption — concerns for the environment and animal welfare. "Both of these issues might be more likely to sway people," write Aaron E. Carroll, MD, MS, and Tiffany S. Doherty, PhD, of the Center for Pediatric and Adolescent Comparative Effectiveness Research at Indiana University School of Medicine in Indianapolis. "And if they result in reducing meat consumption, and some receive a small health benefit as a side effect, everyone wins."

*All study lead authors have reported no relevant financial relationships. Some coauthors have reported various financial ties to the private sector outside the submitted work.*

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***http://bit.ly/2OfOrWi***

## Study explains molecular mechanism of botanical folk medicines used to treat hypertension

### *Lavender, fennel and chamomile among herbs discovered to act upon a shared therapeutic target in blood vessels*

Irvine, Calif. - Common herbs, including lavender, fennel and chamomile, have a long history of use as folk medicines used to lower blood pressure. In a new study, University of California, Irvine researchers explain the molecular mechanisms that make them work.

Published today in Proceedings of the National Academy of Sciences (PNAS), the study illustrates how many of the known traditional botanical plants used to lower blood pressure activate a specific potassium channel (KCNQ5) in blood vessels. KCNQ5, together with other potassium channels including KCNQ1 and KCNQ4, is expressed in vascular smooth muscle. When activated, KCNQ5 relaxes blood vessels, making it a logical mechanism for at

least part of the hypotensive actions of certain botanical folk medicines.

"We found KCNQ5 activation to be a unifying molecular mechanism shared by a diverse range of botanical hypotensive folk medicines. Lavandula angustifolia, commonly called lavender, was among those we studied. We discovered it to be among the most efficacious KCNQ5 potassium channel activators, along with fennel seed extract and chamomile," said Geoff Abbott, PhD, professor of physiology and biophysics at the UCI School of Medicine and senior investigator on the study.

Interestingly, the KCNQ5-selective potassium channel activation feature found in the botanicals is lacking in the modern synthetic pharmacopeia. Until now, it seems to have eluded conventional screening methods utilizing chemical libraries, which may account for why it is not a recognized feature of synthetic blood pressure medications.

"Our discovery of these botanical KCNQ5-selective potassium channel openers may enable development of future targeted therapies for diseases including hypertension and KCNQ5 loss-of-function encephalopathy," said Abbott.

Documented use of botanical folk medicines stretches back as far as recorded human history. There is DNA evidence, dating back 48,000 years, that suggests the consumption of plants for medicinal use by Homo neanderthalensis. Archaeological evidence, dating back 800,000 years, even suggests non-food usage of plants by Homo erectus or similar species. Today, evidence of the efficacy of botanical folk medicines ranges from anecdotal to clinical trials, however the underlying molecular mechanisms often remain elusive.

*This study was supported by the National Institutes of Health, National Institute of General Medical Sciences and the National Institute of Neurological Disorders and Stroke. Also involved in the study were UCI's Rían Manville, PhD, PhD student Kaitlyn Redford and Benjamin Katz, PhD, and from the University of Copenhagen, Denmark, PhD student Jennifer van der Horst and Thomas Jepps, PhD.*

***https://bbc.in/336xHVJ***

## 'Revolutionary' drug for prostate cancer

***Olaparib could become a revolutionary treatment for prostate cancer - the first genetically targeted drug for fighting the disease, say experts.***

The precision medicine is already used by the NHS for ovarian cancer and has been called a game-changer by cancer doctors.

A cancer conference heard how, in trials, it slowed tumour growth in men with advanced prostate cancer. This could improve survival for some men, researchers hope. Experts say it could be made available to patients in the next couple of years. The drug, made by AstraZeneca, was fast-tracked to NHS ovarian cancer patients in England, paid for through the Cancer Drugs Fund, in July.

**Precision medicine**

Olaparib, also called Lynparza, works by targeting and killing cancer cells with faulty genetic code, while sparing normal cells with healthy DNA. It won't work for everyone with prostate cancer, but it is effective for some men with the disease, say researchers.

Patients can be tested to see if they have the genetic errors that the drug can attack - faulty DNA repair genes including BRCA1 and BRCA2. This precision approach means the patients most likely to benefit will be treated, sparing them potential side-effects from other drugs that may not work as well for them.

In the trial, doctors compared olaparib with two other commonly prescribed prostate drugs (hormone treatments called abiraterone and enzalutamide).

It appeared to delay cancer growth by months, which researchers say should hopefully mean men can survive for longer even when their disease is advanced. They will be monitoring patients to confirm this.

## About prostate cancer

***One in eight men will be diagnosed with prostate cancer in their lifetime. It mainly affects men over the age of 50 and the risk increases with age.***

***Not all of these tumours need immediate treatment. If the cancer is at an early stage and not causing symptoms, doctors may instead suggest careful monitoring.***

***Some cases are more aggressive and need treatment but can be cured if caught early enough.***

***Other cases may only be diagnosed at a late stage when the cancer has spread and cannot be cured.***

***All treatments, including olaparib, can have side-effects.***

***Doctors can talk advise patients about what might be the best treatment for them.***

Prof Johann de Bono, from the Institute of Cancer Research, London, who co-led the drug trial, said: "It's essential that we become smarter in the way we treat prostate cancer, so that every man gets the treatment that will be of greatest benefit for them."

Dr Matthew Hobbs, from the charity Prostate Cancer UK, said: "This hugely exciting result represents a revolution in the treatment of prostate cancer. It finally brings prostate cancer medicine into the 21st Century by giving us, for the first time ever, a therapy that makes use of genetic testing of the tumour to work out which men will benefit.

"This kind of precision medicine approach is already used to treat other cancers, and we hope olaparib will become the first of many treatments for prostate cancer which are based on this sort of detailed understanding of an individual man's tumour."

Prof Nicholas James from Cancer Research UK said: "Tailoring cancer treatment according to a tumour's specific genetic faults is a core part of care in breast, lung or skin cancers to name a few, and has helped us give patients the treatments that are most likely to work for them. But with prostate cancer, we've been treating everyone the same way.

"Matching patients to the most appropriate treatment for their tumour type could radically change the way we treat prostate cancer. In this case, olaparib only slowed the disease down for a few months in a subset of men, but the approach itself is full of possibilities. And if we get to a point where we can tailor treatments in prostate cancer from an early stage, we can give every patient the best chance of being successfully treated."

***http://bit.ly/2VdBFJb***

## Interstellar Comet 2I/Borisov Probably Came from Double Red Dwarf Kruger 60

***Suggestions that the interstellar comet 2I/Borisov likely came from a binary star system called Kruger 60***

**by Sergio Prostak**

A new study by astronomers from the A. Mickiewicz University and the Space Research Centre of the Polish Academy of Sciences suggests that the interstellar comet 2I/Borisov likely came from a binary star system called Kruger 60.

Kruger 60 is a visual binary stellar system located in the constellation of Cepheus. Also known as DO Cephei, HD 239960, Gliese 860, BD+56 2783, HIP 110893, and ADS 15972, it is a tenth closest multiple stellar system, currently only 13.15 light-years from the Sun and approaching. Kruger 60 is named after the German astronomer Adalbert Kruger who observed it in 1873.

It consists of two M-type stars (red dwarfs) — Kruger 60A and B — that orbit each other once every 44.6 years.

Kruger 60A has about 27% of the Sun's mass and 35% of the solar radius, Kruger 60B is a smaller star with about 18% of the Sun's mass and 24% of the solar radius.

Dr. Piotr Dybczynski from the Astronomical Observatory Institute at the A. Mickiewicz University and colleagues found that Kruger

60 is a good candidate for a home system of 2I/Borisov, a comet of interstellar origin discovered on August 30, 2019. The astronomers analyzed 548 observations of the interstellar comet available from the Minor Planet Center at the International Astronomical Union.

They modeled the motion of the comet, the Sun and 647 stellar systems from their list of potential perturbers of cometary motion.

They found that one million years ago, 2I/Borisov passed Kruger 60 at a distance of 5.7 light-years having an extremely small relative velocity of 7,700 mph (3.43 km/s).

"As the orbit of this comet will become more precise the minimal distance between these two bodies might vary but their relative velocity will remain very small, which suggests that 2I/Borisov might originate from Kruger 60," the researchers said.

Their paper was posted to arXiv.org on September 24, 2019.

***Piotr A. Dybczynski* et al. *2019. Kruger 60 — a plausible home system of the interstellar comet C/2019 Q4. arXiv: 1909.10952***

***http://bit.ly/2OnBvh1***

## Could the female orgasm be a happy remnant of evolution?

### *Have scientists solved the mystery of the female orgasm?*

As a team of researchers pointed out, during intercourse the male orgasm serves an obvious reproductive function: Without it, ejaculation can't happen.

But the reproductive role of female orgasm has been much less clear, because ovulation in humans occurs whether a woman has recently had an orgasm or not. So the very existence of the female orgasm in women has long been a physiological mystery. But now U.S. researchers (with the help of some sexually active rabbits) believe they may have solved this riddle.

The new research was led by Gunter Wagner, a professor of ecology and evolutionary biology at Yale, and Mihaela Pavlicev, an assistant professor of pediatrics at the University of Cincinnati.

According to the investigators, part of the puzzle has been that the clitoris—the central locus for the female orgasm—is located a good distance above where the real "action" of reproductive intercourse occurs.

That led the team to look further back in the mammalian family tree. And as the two scientists reported in the Sept. 30 issue of the *Proceedings of the National Academy of Sciences*, the clitoris *is* much more central to intercourse for animals such as cats, rabbits and ferrets. In those mammals, the clitoris is located along the reproductive pathway used for intercourse. In fact, in female rabbits, clitoral stimulation and orgasm is actually required to initiate the ovulation needed to reproduce.

That's different from what happens in women, of course. So Wagner and Pavlicev theorized that, somewhere along the evolutionary timeline, the clitoris migrated away from the center of reproductive activity while retaining its ability to release pleasure-inducing hormones.

To test out their theory that the female orgasm is essential to procreation—at least in other mammals—the two scientists injected the anti-depressant fluoxetine (best known as Prozac) into female rabbits. Since the drug is known to deplete a woman's ability to orgasm, the researchers theorized that, by extension, rabbits who got the shot might be less likely to ovulate.

And that was the case: As the female rabbits' ability to orgasm foundered, they ovulated 30% less often, compared to females that didn't get the antidepressant.

That seemed to confirm the notion that, in humans' distant evolutionary past at least, the female orgasm was essential to creating new offspring. "This is important to our understanding female sexuality," Wagner said in a Yale news release. The finding also rebuts notions promulgated by Sigmund Freud and others that women who fail to reach orgasm are somehow psychologically

immature or saddled with second-rate sexual partners. "If this theory is correct," said Wagner, "none of those older ideas are valid."

***More information:*** *Mihaela Pavlicev et al. An experimental test of the ovulatory homolog model of female orgasm, Proceedings of the National Academy of Sciences (2019). DOI: 10.1073/pnas.1910295116*

***http://bit.ly/2LLBcuS***

## 'Trippy' Bacteria Engineered to Brew 'Magic Mushroom' Hallucinogen

***Scientists modified E. coli to produce the psychoactive chemical that makes 'shrooms so trippy.***

**By Nicoletta Lanese - Staff Writer 4 days ago Health**

Scientists have transformed a common bacterial cell into a psychedelic "drug factory" capable of pumping out copious quantities of psilocybin, the chemical famously found in "magic mushrooms," according to a new study.

Psilocybin can be found in more than 100 'shroom species, most notably in one called *Psilocybe cubensis*, which has a domed cap and skinny stem. Although best known for inducing mind-bending hallucinations, psilocybin is currently being tested as a potential treatment for several psychiatric conditions, including addiction, major depressive disorder and post-traumatic stress disorder, according to ClinicalTrials.gov. If 'shroom-based drugs ever come to market, scientists will need a better method for harvesting psilocybin than farming tons of fungi, the authors said.

So, the researchers turned to bacteria, which can be engineered to churn out chemicals in high amounts. Some medications — including the hormone insulin — are already produced with the help of genetically engineered bacteria.

In the new study, the Miami University, researchers manipulated the metabolism of the bacteria *Escherichia coli*, so that its cells began producing psilocybin.Later, the research team scaled up production to brew the hallucinogen in huge batches, according to a statement from the university.

"We are taking the DNA from the mushroom that encodes its ability to make this product and putting it in *E. coli*," study co-author Andrew Jones, a professor of chemical and biological engineering, said in the statement. The team developed multiple strains of psychedelic *E. coli* and tested what environmental conditions — temperature, nutrients, culture medium — were required to consistently produce high concentrations of psilocybin with few unwanted side products. The team eventually selected the most efficient strain, dubbed pPsilo16, and cultivated it in a bioreactor for mass production, according to the study, published online Sept. 21 by the journal Metabolic Engineering.

"What's exciting is the speed at which we were able to achieve our high production," Jones said. Over the course of the 18-month-long study, the researchers were able to increase production by 500-fold. According to the authors, their *E. coli* produced more psilocybin than any other organism retrofitted with "magic mushroom" DNA to date. The scientists assert that their results provide compelling evidence that psilocybin could be produced on an industrial scale for use in psychiatric medications.

***http://bit.ly/31O0s9r***

## When Humans Hear Music, Monkeys May Hear Noise

***The auditory cortices of humans and rhesus monkeys respond very differently to harmonic tones.***

**Katarina Zimmer**

If there's one thing Bevil Conway has learned from studying the visual cortices of rhesus macaques, it's that they're remarkably like those of humans. The visual cortex is anatomically highly similar in the two species, and macaques and humans show comparable behavioral and neural responses to colors and images. When a macaque opens its eyes, "I'm pretty sure he's seeing what I'm

seeing," says Conway, a neuroscientist at the National Institutes of Health (NIH) in Bethesda, Maryland. But does the same hold true for what he hears?

The question came up in 2014 over a beer with Sam Norman-Haignere, then a graduate student with Josh McDermott and Nancy Kanwisher at MIT, where Conway headed a lab at the time. Norman-Haignere told Conway about his groups' recent collaborative finding that a particular patch of the human auditory cortex is more sensitive to harmonic tones—notes that have an easily discernible pitch, such as those played on a piano—than to noisy sounds, such as those made by a drum. When a dozen people listened to harmonic tones in a functional magnetic resonance imaging (fMRI) scanner, this patch of the auditory cortex flared up with heightened neural activity—substantially more than when the participants listened to noise.

Musing whether there was an equivalent region in monkeys that would also respond selectively to harmonic tones over noise, Conway and Norman-Haignere made a bet. "I thought, I'm pretty sure that monkeys are going to have that," Conway recalls. Given that the visual systems of humans and macaques are so similar, he figured that their auditory cortices would be as well. Norman-Haignere wasn't so sure. Humans rely on harmonic tones not only in music, but also to articulate vowels in spoken language. Because monkeys lack these cultural aspects, the animals may not need a brain region devoted to perceiving harmonic sounds, reasoned Norman-Haignere, who is now a postdoc at Columbia University.

Along with McDermott and Kanwisher, the two researchers set out to repeat Norman-Haignere's earlier experiments, this time comparing the human brain's response to that of the macaque (*Macaca mulatta*). To find out if the two species' auditory cortices respond selectively to harmonic tones, the researchers used computer software to synthesize two sets of sounds. The first set of stimuli was harmonic, based on short sequences of up to a dozen notes differing in melody and the range of audio frequencies—that is, the range from the lowest note to the highest note in the sequence. The second, control set of stimuli was noisy, created from a scrambled kind of sound much like static on the radio or TV. The team designed the noise to match the frequency ranges of the harmonic stimuli and thus ensure that the sound sets were comparable.

Three macaques and four people took their turn in an fMRI machine as the scientists played the sounds inside the scanner and monitored each participant's auditory cortex. As observed in the earlier experiments, the human auditory cortex showed significantly greater activity in response to the harmonic stimuli than to the noise. But to Conway's surprise, the same brain region in macaques showed no significant differences in response to the two sets of sounds. In fact, if anything, the monkeys' brains often had a greater response to noise than to harmonic tones.

The contrast between macaques and humans couldn't have been clearer, Conway says, "but then we had to spend about two years full-time collecting data in order to convince ourselves that the result was real."

Initially, the team wondered whether the monkeys' lack of selective response to sounds with a specific pitch could be simply due to their unfamiliarity with synthetic sounds. So the researchers repeated the same experiment, this time playing recordings of real macaque calls and computationally engineered, pitch-less, or noisy, versions of those vocalizations. Even then, the fMRI results revealed that human auditory cortices were much more sensitive to the pitch quality of those sounds than macaque brains were. "I think I owe Sam a beer," Conway remarks.

What makes the finding all the more surprising is that macaque brains are perfectly capable of detecting differences in audio

frequency. Like humans, macaques have a “tonotopic map” in their auditory cortex, a pattern of brain regions in which each region responds to a specific range of frequencies, although the team’s fMRI data, consistent with earlier research, indicate that this map is arranged slightly differently in macaques than it is in humans. The monkeys just don’t show a preference for sounds with a specific pitch in the way that humans do.

To Conway, the findings may explain why previous researchers have so far failed to find neurons that respond selectively to sounds with pitch in macaques, and have had a hard time training macaques and other monkey species, such as capuchins, to perform certain auditory tasks that humans excel at. “The explanation has historically been that the monkeys’ memory cortex works differently, but our findings say no, maybe their memory systems are just fine, but the auditory cortex works differently.”

The heightened responsiveness of the human brain to pitch may well have to do with the origins of spoken language as well as music. “Harmonic structures are very important to humans,” says Charles Snowdon, a primatologist who recently retired from the University of Wisconsin–Madison. “We’re producing very clear harmonics [with] every vowel sound that we use, and we can’t speak without producing vowels.”

Macaques do use some harmonic vocalizations, for friendly calls and chatter in particular, but they use them far less frequently than do humans. “The macaques make a greater use of noisy signals and noisy vocalizations in their own communication and therefore it makes sense that they would have significant amounts of brain tissue devoted to processing noise,” Snowdon says. Humans can make vocalizations that are noisy too—such as growling—but they are rarely used, “because we have language instead,” he adds.

But whether humans are unique among primates in having a preference for harmonic sounds—what Conway and his colleagues call “pitch bias”—will require further research in other primate species, Snowdon says. Conway and his colleagues plan on examining tamarin monkeys (genus *Saguinus*) next, which make many vocalizations that have harmonic structure.

For now, Conway is left to wonder what a macaque’s experience of the acoustic world may be. What would music sound like to a macaque? It’s impossible to say, but he imagines a recent performance by Hong Kong musical artist Samson Young might offer one indication. Young had an orchestra play a “muted” version of Russian composer Tchaikovsky’s Fifth Symphony. “He taped all of the strings on the instruments so they couldn’t make any pitches, and all that’s recorded is the noise,” Conway says—the swishing and tapping of bows against tape. “I think that’s probably what it sounds like to the monkey.”

***http://bit.ly/353h3Il***

## Science proves that what doesn't kill you makes you stronger

***Causal relationship between failure and future success***

Scientists at Northwestern University's Kellogg School of Management have established a causal relationship between failure and future success, proving German philosopher Friedrich Nietzsche's adage that "what does not kill me makes me stronger."

The researchers utilized advanced analytics to assess the relationship between professional failure and success for young scientists. They found, in contrast to their initial expectations, that failure early in one's career leads to greater success in the long term for those who try again.

"The attrition rate does increase for those who fail early in their careers," lead author Yang Wang said. "But those who stick it out, on average, perform much better in the long term, suggesting that if it doesn't kill you, it really does make you stronger."

The study, "Early-career setback and future career impact," will be published Oct. 1, in *Nature Communications*.

The findings provide a counter-narrative to the Matthew Effect, which posits a "rich get richer" theory that success begets more success. "It turns out that, historically, while we have been relatively successful in pinpointing the benefits of success, we have failed to understand the impact of failure," said Dashun Wang, corresponding author and associate professor of management and organizations at Kellogg.

**Methodology and findings**

Researchers analyzed records of scientists who, early in their careers, applied for R01 grants from the National Institutes of Health (NIH) between 1990 and 2005. They utilized the NIH's evaluation scores to separate individuals into two groups: (1) the "near-misses" whose scores were just below the threshold that received funding and (2) the "just-made-its" whose scores were just above that threshold. Researchers then considered how many papers each group published, on average, over the next 10 years and how many of those papers turned out to be hits, as determined by the number of citations those papers received.

Analysis revealed that individuals in the near-miss group received less funding, but published just as many papers, and more hit papers, than individuals in the just-made-it group.

The researchers found that individuals in the near-miss funding group were 6.1% more likely to publish a hit paper over the next 10 years compared to scientists in the just-made-it group.

"The fact that the near-miss group published more hit papers than the just-made-it group is even more surprising when you consider that the just-made-it group received money to further their work, while the near-miss group did not," said Benjamin Jones, study co-author and the Gordon and Llura Gund Family Professor of Entrepreneurship at Kellogg.

Researchers wondered whether the effect could be attributed to a "weed-out" phenomenon—that the early-career failure caused some scientists in the near-miss group to exit the field, leaving only the most-determined members. Further analysis revealed that while the attrition rate after failure was 10 percent higher for the near-miss group, that alone could not account for the greater success later in their careers.

After testing a number of other possible explanations for the long-term success of the near-miss group, researchers could not find any supporting evidence for any of their hypotheses, suggesting other unobservable factors, such as grit or lessons learned, might be at play. The research does not contradict the Matthew Effect, but rather suggests a complementary path for those who fail.

"There is value in failure," Dashun Wang said. "We have just begun expanding this research into a broader domain and are seeing promising signals of similar effects in other fields."

All three researchers involved in the study are faculty in Northwestern's Center for the Science of Science and Innovation, which is dedicated to understanding the conditions that lead to scientific success and failure.

***More information:*** *Nature Communications (2019). DOI: 10.1038/s41467-019-12189-3*

***http://bit.ly/2IoAHEI***

## Tsunami dumped tropical disease on North American coastline

***Scientists solve a riddle and sound a warning.***

**Mark Bruer reports.**

The potentially fatal fungus *Cryptococcus gattii* could have been transmitted to the Pacific Northwest via tsunami, sounding an alarm for more recent seismic events.

When a deadly tropical infection appeared on the chilly west coast of North America in 1999, its origin was a mystery. Now, researchers believe a giant earthquake 35 years earlier was to blame.

More than 300 people have been hit by a mysterious outbreak of *Cryptococcus gattii* fungal infection in the Pacific Northwest over the past 20 years, with cases still occurring in humans and wildlife.

Before then, *C. gattii* had been confined almost entirely to South America, Papua New Guinea and Australia.

The fungus typically infects people through inhalation. It produces a pneumonia-like illness, and may also spread to the brain, causing potentially fatal meningoencephalitis. Published case reports suggest a mortality rate of more than 10 percent.

How this nasty tropical disease reached the cool shores of North America has puzzled epidemiologists since the first cases appeared on Vancouver Island.

Theories to explain its presence have included global warming and the import of tropical eucalyptus trees.

But researchers at the Johns Hopkins Bloomberg School of Public Health and the nonprofit Translational Genomics Research Institute now believe they have the answer: it's due to a chain of events involving a canal, shipping movements, an earthquake, and the recent evolution of the fungus itself.

The trouble may have started when the Panama Canal opened in 1914, increasing shipping significantly between Atlantic and Pacific ports. This, the researchers write in *mBio*, brought *C. gattii* from south to north, possibly in ships' ballast tanks. Ships in those days routinely took on water in one port and simply discharged it, without treatment, in another.

This part of the theory is supported by a "molecular clock" analysis of the DNA sequence of the *C. gattii* fungus subtypes found in North America, which shows they would have arrived from Brazil or nearby between 60 and 100 years earlier.

So how did *C. gattii* come to colonise the west coast of Canada and the United States?

This is where the Great Alaskan Earthquake of 1964 comes in.

The 9.2 quake of 1964 is the largest recorded in the northern hemisphere, and its effects were felt as far away as Hawaii. It now seems that one of its unseen effects was to carry the fungus to shore on a series of tsunamis.

The quake had its epicentre in southeastern Alaska but spawned tsunamis throughout the North Pacific. These inundated coastal areas of British Columbia, Washington, Oregon, and California. The affected regions correspond broadly to the locations where *C. gattii* has been found and human infections have occurred.

But that was in 1964 – decades before the first infection in humans. Why did it take so long to emerge?

The researchers have found evidence that *C. gattii* can evolve potent defences as a result of being preyed on in the wild by amoebas – defences that can make it more virulent when it infects people. Report co-author Arturo Casadevall says it appears the fungus may have spent 35 years quietly evolving to a more dangerous form to survive in its new home.

"*C. gattii* may have lost much of its human-infecting capacity when it was living in seawater, but then when it got to land, amoebas and other soil organisms worked on it for three decades or so until new *C. gattii* variants arose that were more pathogenic to animals and people.

"The big new idea here is that tsunamis may be a significant mechanism by which pathogens spread from oceans and estuarial rivers onto land and then eventually to wildlife and humans.

"If this hypothesis is correct, then we may eventually see similar outbreaks of *C. gattii*, or similar fungi, in areas inundated by the 2004 Indonesian tsunami and 2011 Japanese tsunami."

http://bit.ly/2Mjhvt8

# Human Reference Genome Doesn't Capture Full Genetic Diversity

***A new analysis of 1,000 Swedes uncovers a chromosome's worth of novel DNA sequences—much of them ancient—underscoring the need for a more diverse reference genome.***

**Katarina Zimmer**

It's hard to find a word in the dictionary if some pages are missing. Similarly, it's hard to study genetic sequences if they're absent from the human reference genome, the product of the $2.7 billion Human Genome Project, which is typically used as a guide for genomic studies.

A new study has identified more than 61,000 novel genetic sequences across 1,000 Swedish genomes that are absent from the human reference genome. Many of these sequences were also found in African and Icelandic genomes, and even the chimpanzee genome, suggesting they are ancient. The findings, published last week (September 24) in *Molecular Biology and Evolution*, highlight the diversity of human DNA and underscore the need for an improved reference genome that's more representative of human genetic variation.

"It's part of a family of papers that make relatively similar points," remarks Jesse Gillis, a computational biologist at Cold Spring Harbor Laboratory who wasn't involved in the research. "It's about the reference [genome] not being reflective of what is very common in the human population."

Anna Lindstrand, a clinical geneticist at the Karolinska Institute and the senior author of the new research, is well acquainted with the reference genome's poor representation of Swedes. Her diagnostic lab at the Karolinska University Hospital often performs genetic screens on patients to find disease-causing mutations. To do that, they sequence the patients' DNA and align it with the human reference genome—considered to be a "normal" genome, she says—and compare changes relative to it.

However, most of the reference genome stems from a single individual. In addition, the genome may have gaps because the methods used to assemble it could have missed some hard-to-catch DNA segments. If a patient has a particular genetic mutation that can't be found in the reference genome, that would suggest the mutation is unusual—but it may in fact be quite common across many individuals, Lindstrand explains.

To get a better idea of how much genetic variation in the Swedish population is captured by the reference genome, Lindstrand and her colleagues sequenced the genomes of 1,000 people from across Sweden. They then used a computational pipeline built by Lindstrand's graduate student Jesper Eisfeldt to assemble these genomes from scratch, rather than by aligning them to the human reference genome.

In comparing each newly assembled genome to the reference genome they found the Swedish ones contained 1.8 megabases of genetic material that could not be mapped to GRCh37—a 2009 version of the human reference genome that is often used by clinicians. Nearly 40 percent of that genetic material also couldn't be matched to GRCh38, a newer version of the human reference genome.

In total, across the 1,000 newly assembled genomes, the researchers counted 61,044 sequences—enough DNA to fill up chromosome 21—that were absent from either reference genome, making them "novel sequences."

Some of the novel sequences were common, but most of them were relatively rare across the study population, a fascinating aspect of the study to Lindstrand. "Even though we humans are so similar, there's also so much diversity," she remarks.

The novel sequences were scattered across the genomes of Swedish individuals—in genes as well as in non-coding regions. Notably, the team found handfuls of them within human disease-causing genes, she says.

"These are sequences that we don't interrogate today because they are not in the human reference genome—so if they are somehow linked to disease, we wouldn't know about it."

The findings didn't surprise Lindstrand: Previous studies of African and Icelandic populations have also discovered novel sequences not present in the reference genome. To understand the origin of the novel sequences found in Swedish DNA, Lindstrand's team compared them with those in African and Icelandic genomes and found that many were shared between Swedish, African, and Icelandic DNA.

There were still some novel sequences that didn't align to the other human populations, so the team looked for them in the chimpanzee genome. They found that 31 percent of the Swedish novel sequences were only present in the chimpanzee genome and not in any other human genome, suggesting that they are ancient.

Perhaps those sequences were lost in the human reference genome due to a technical artifact, suggests Peter Audano, a bioinformatician at the University of Washington who wasn't involved in the study. Or, perhaps more likely, the reference genome and other human populations deleted those ancestral sequences during human evolution, he says.

**Toward an improved reference genome**

Neither Gillis nor Audano are surprised by the findings. The human reference genome is stitched together from multiple individuals, but 70 percent of it is derived from a single person, Audano says. "That one person can't represent all the diversity out there. There's quite a bit of diversity that you're just not going to find in any given individual," he says.

Audano notes that the team used Illumina sequencing for its study, which isn't the best method to get a good resolution of a given genome.

It only sequences very short snippets of DNA at a time and is known to miss repetitive sequences and duplications. Long read technologies, which sequence longer strands of DNA at a time, are necessary to bridge those regions (which is why the National Institutes of Health is funding a modernization of the human reference genome using long read sequencing of 350 individuals.) However, studies like Lindstrand's that are based on short read technologies are helpful in surveying genetic diversity across many individuals quickly and cost-effectively, he notes.

Lindstrand views constructing a new type of reference genome—a graph reference genome—as a good potential solution. This would use a normal reference genome as a backbone of a "graph" to which common genetic variants are added, in order to encompass as much variation as possible.

Gillis favors incremental improvement to the reference genome over drastic changes. "I am nervous about changing the reference too dramatically" because it will require so much change in methods and techniques used by downstream research communities that use the reference, he says. "Graph genome methods might be perfect if they worked perfectly, but that might be tricky to make happen."

Regardless of how researchers decide to alter the reference genome, improvements will have many benefits to science, Lindstrand stresses. "By improving the reference, we will diagnose more patients and that will be very beneficial to the medical community when we move towards personalized medicine," she adds.

*J. Eisfeldt et al., "Discovery of novel sequences in 1,000 Swedish genomes,"* **Molecular Biology and Evolution**, *doi:10.1093/molbev/msz176, 2019.*

http://bit.ly/31QxKo7

# Experts advise against routine bowel cancer testing for all over-50s

***Only those at higher risk should consider screening, advises panel***

Routine testing for bowel cancer should not be recommended for everyone aged 50-79 years because, for those at very low risk, the benefit is small and uncertain and there are potential harms, say a panel of international experts in The BMJ today. But they say screening should be recommended for men and women with a risk of 3% or more in the next 15 years, as this is the point at which the balance of benefits and harms tilts in favour of screening.

Their advice is based on the latest evidence and is part of *The BMJ*'s 'Rapid Recommendations' initiative - to produce rapid and trustworthy guidance based on new evidence to help doctors make better decisions with their patients.

Bowel (colorectal) cancer is a common type of cancer in men and women - about 1 in 20 people in most high income countries will get it during their lifetime. A person's risk depends on their age, sex, genetics and lifestyle factors, such as alcohol intake, smoking, physical activity and diet.

Most guidelines recommend screening for everyone from age 50, irrespective of their individual risk. At this age, the risk of developing bowel cancer over the next 15 years is typically 1-2%, meaning that in a group of 100 people with the same risk factors, one or two will develop bowel cancer within the next 15 years.

The four most common screening options are home faecal testing (FIT) every year or every two years, sigmoidoscopy (examination of the lower colon) or colonoscopy (examination of the entire colon) done at a clinic or hospital.

Recently published research on the long term effects of bowel cancer screening has shed new light on the benefits and harms, and has the potential to change current recommendations.

So an international panel made up of researchers, clinicians and patients, reviewed the evidence base, including this new evidence, to evaluate the benefit-to-harm balance of screening using a "risk based approach."

This means they took account of an individual's cumulative risk of bowel cancer over the next 15 years together with risk of harm from the procedure (e.g. bowel perforations, unnecessary treatment) and quality of life (e.g. anxiety, burden of procedure), as well as a person's values, preferences, and life expectancy.

Their recommendations apply to healthy individuals aged 50-79 years with a life expectancy of at least 15 years.

For men and women with an estimated 15-year bowel cancer risk below 3%, they suggest no screening, and say most informed individuals in this group are likely to decline screening.

However, for men and women with an estimated 15-year bowel cancer risk above 3%, they suggest screening with one of the four options, and say most informed individuals in this group are likely to choose screening after discussing the potential benefits and harms with their doctor.

The panel does not recommend any one test over another, but they found convincing evidence that people's values and preferences on whether to test and what test to have varies considerably.

For example, some people will want to avoid an invasive test like colonoscopy, and may prefer faecal testing. While those who most value preventing bowel cancer or avoiding repeated testing are likely to choose sigmoidoscopy or colonoscopy.

The authors stress that there are still many uncertainties in terms of what is the most effective screening test or combination of tests, and at what age and interval they should be used, and suggest this should be the focus of future research. These recommendations may also be altered as new evidence emerges, they conclude.

The evidence backing colorectal cancer screening "is still fragile and strong recommendations cannot be issued at the moment," writes Professor Philippe Autier at the International Prevention Research Institute (iPRI) in a linked editorial.

He welcomes the shift away from maximizing uptake of screening to a personalised approach based on individual risk and informed choice, which he says has several advantages over offering screening to everyone in eligible age groups.

He also acknowledges that new research is warranted for refining risk based recommendations, and says "better knowledge of risk factors associated with late stage at diagnosis and colorectal cancer death is likely to improve risk based approaches."

***http://bit.ly/2Vcwh9o***

## Aspirin may prevent air pollution harms

### *NSAIDs may lessen the adverse effects of air pollution exposure on lung function*

A new study is the first to report evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin may lessen the adverse effects of air pollution exposure on lung function. The team of researchers from the Columbia Mailman School of Public Health, Harvard Chan School of Public Health, Boston University School of Medicine published their findings in the *American Journal of Respiratory and Critical Care Medicine*.

The researchers analyzed a subset of data collected from a cohort of 2,280 male veterans from the greater Boston area who were given tests to determine their lung function. The average age of participants was 73 years. The researchers examined the relationship between test results, self-reported NSAID use, and ambient particulate matter (PM) and black carbon in the month preceding the test, while accounting for a variety of factors, including the health status of the subject and whether or not he was a smoker.

They found that the use of any NSAID nearly halved of the effect of PM on lung function, with the association consistent across all four weekly air pollution measurements from same-day to 28 days prior to the lung function test.

Because most of the people in the study cohort who took NSAIDs used aspirin, the researchers say the modifying effect they observed was mainly from aspirin, but add that effects of non-aspirin NSAIDs are worthy of further exploration. While the mechanism is unknown, the researchers speculate that NSAIDs mitigate inflammation brought about by air pollution.

"Our findings suggest that aspirin and other NSAIDs may protect the lungs from short-term spikes in air pollution," says first and corresponding author Xu Gao, PhD, a post-doctoral research scientist in the Department of Environmental Health Sciences at the Columbia Mailman School. "Of course, it is still important to minimize our exposure to air pollution, which is linked to a host of adverse health effects, from cancer to cardiovascular disease."

"While environmental policies have made considerable progress toward reducing our overall exposure to air pollution, even in places with low levels of air pollution, short-term spikes are still commonplace," says senior author Andrea Baccarelli, MD, PhD, chair of the Department of Environmental Health Sciences at the Columbia Mailman School. "For this reason, it is important to identify means to minimize those harms."

An earlier study by Baccarelli found that B vitamins may also play a role in reducing the health impact of air pollution.

*Co-authors include Brent Coull, Xihong Lin, and Joel Schwartz at Harvard; and Pantel Vokonas at the Boston University School of Medicine.The current study was supported by grants from the National Institute of Environmental Health Sciences (ES009089, ES021733, ES025225, ES027747). The VA Normative Aging Study is supported by the Cooperative Studies Program/Epidemiology Research and Information Center of the U.S. Department of Veterans Affairs and is a component of the Massachusetts Veterans Epidemiology Research and Information Center in Boston.*

http://bit.ly/35ecJpR

# Researchers repurpose failed cancer drug into printable semiconductor

***Repurposing a failed cancer drug into a new type of organic semiconductor for use in transistors and chemical sensors.***

CHAMPAIGN, Ill. -- Many potential pharmaceuticals end up failing during clinical trials, but thanks to new research from the University of Illinois, biological molecules once considered for cancer treatment are now being repurposed as organic semiconductors for use in chemical sensors and transistors. The researchers report their findings in the journal Nature Communications.

Organic semiconductors are responsible for things like flexible electronics and transparent solar cells, but researchers are working to expand their use in biomedicine and devices that require interaction between electrically active molecules and biological molecules.

Chemical and biomolecular engineering professor Ying Diao said she was surprised when the two avenues of her research - pharmaceutical development and printable electronics - merged in her lab with the discovery of semiconductorlike features in a well-studied bioactive molecule. The molecule, which inserts itself into DNA to prevent replication, was once explored as a potential anti-cancer agent.

"This convergence of my two research areas was totally unexpected," Diao said. "While examining these pharmaceutical molecules, we noticed that their molecular structures looked much like the organic semiconductors we were working with in the rest of my group."

These molecules, called DNA topoisomerase inhibitors, are flat and contain neatly stacked columns of electrically conductive molecular rings - features that make a good semiconductor. Distinct from a typical semiconductor, these molecular columns are linked together by hydrogen bonds that can move charges from column to column, forming bridges that transform the entire molecular assembly into a semiconductor - something rarely seen before this study, the researchers said.

"These molecules can interact with biological material with high specificity, making them good candidates for use in biosensors," Diao said. "They are also easily printable but will require new solvents because they are chemically different than other organic semiconductors. The fabrication infrastructure is already in place."

The team printed and tested the semiconductors and acknowledge that their efficiency and performance need improvement. Diao said the real excitement regarding this advance will come from the possibility of discovering similar molecules.

"We envision partnering with researchers in machine learning who can train computers to spot the unique characteristics of these molecules," Diao said. "They can mine the vast pharmaceutical databases available today in search of molecules with similar, or maybe even better semiconducting properties."

*The Shen Postdoctoral Fellowship of the School of Chemical Sciences at the U. of I. and the National Science Foundation - Illinois Materials Research Science and Engineering Center supported this research.*

*The paper "Repurposing DNA-binding agents as H-bonded organic semiconductors" is available online and from the U. of I. News Bureau. DOI: 10.1038/s41467-019-12248-9*

http://bit.ly/336PHzq

# The propensity to hear 'voices' in Schizophrenia may be established by infancy

***The vulnerability to develop "voices" is probably established many years before symptoms begin***

Some people suffering from severe mental illness, particularly schizophrenia, hear "voices," known as auditory hallucinations. This symptom, which afflicts more than 80% of patients, is among the most prevalent and distressing symptoms of schizophrenia.

Patients "hear voices" speaking to them or about them without anyone actually being there. Auditory hallucinations, which usually begin in adolescence and young adulthood, "sound" very real to patients and can have a devastating impact on their quality of life because the "voices" are typically distressing and distracting, sometimes compelling the sufferer into suicidal or violent actions. Uncovering the biological origins of auditory hallucinations is essential for reducing their contribution to the disease burden of schizophrenia.

To investigate the biological origins of hearing "voices" in patients with schizophrenia, a team led by researchers at the Icahn School of Medicine at Mount Sinai used ultra-high field imaging to compare the auditory cortex of schizophrenic patients with healthy individuals. They found that schizophrenic patients who experienced auditory hallucinations had abnormal tonotopic organization of the auditory cortex. Tonotopy is the ordered representation of sound frequency in the auditory cortex, which is established in utero and infancy and which does not rely on higher-order cognitive operations. The study findings, which appears this week in the Nature Partner Journal NPJ Schizophrenia, suggest that the vulnerability to develop "voices" is probably established many years before symptoms begin.

"Since auditory hallucinations feel like real voices, we wanted to test whether patients with such experiences have abnormalities in the auditory cortex, which is the part of the brain that processes real sounds from the external environment," says Sophia Frangou, MD, PhD, Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai. "

Specifically, the research team used an ultra-high field scanner with a powerful 7 Tesla magnet to obtain high-resolution images of brain activity while study participants listened passively to tones across a range of very low to very high frequencies. In healthy brains, these sounds are processed in a very organized fashion; each frequency activates a specific part of the auditory cortex forming a tonotopic map. The team obtained tonotopic maps from 16 patients with schizophrenia with a history of recurrent auditory hallucination and 22 healthy study participants. They found that patients showed greater activation in response to most sound frequencies. Additionally, the mapping of most sound frequencies to parts of the auditory cortex appeared "scrambled" in patients with schizophrenia, suggesting that the normal processes for the organized representation of sound in the brain are disrupted in schizophrenia.

"Because the tonotopic map is established when people are still infants and remains stable throughout life, our study findings suggest that the vulnerability to develop "voices" is linked a deviance in the organization of the auditory system that occurs during infancy and precedes speech development and the onset of psychotic symptoms by many years. This is particularly exciting because it means that it might be possible to identify potential vulnerable individuals, such as the offspring of schizophrenia patients, very early on."

According to the authors, in addition to helping doctors spot people who are likely to experience hallucinations before the symptoms appear or become severe, the auditory cortex may be an area of consideration for novel neurmodulation methods to help patients who already have symptoms.

Looking ahead, Dr. Frangou's research team will replicate and expand the current observations in larger samples to determine their relevance to hallucinations across diagnoses and to quantify the association of tonotopic disruption to auditory cortical activation and connectivity during actual hallucinatory experiences.

*The study was supported by the National Institutes of Mental Health, the National Cancer Institute, The Netherlands Organisation for Health Research and Development, the Stanley Foundation and the Brain and Behavior Research Foundation.*

http://bit.ly/30NVjq3

# Fungal invasion of pancreas creates cancer risk

***Certain fungi move from the gut to the pancreas, expand their population more than a thousand-fold, and encourage pancreatic cancer growth, a new study finds.***

Published online in *Nature* October 2, the study is the first to offer strong evidence that the mycobiome - the local mix of fungal species in the pancreas - can trigger changes that turn normal cells into pancreatic ductal adenocarcinoma or PDA. This form of cancer is usually deadly within two years.

Conducted in mice and in patients with pancreatic cancer, the study found that fungal species travel into the pancreas up the pancreatic duct, a tube through which digestive juices drain in the opposite direction into the intestines. The study authors say this exchange results in abnormal fungal populations in both the gut and pancreas in the presence of PDA. Led by researchers from the NYU School of Medicine and the NYU College of Dentistry, the study also found that treating mice with a potent antifungal drug reduced their PDA tumor weight over the 30 weeks by 20 to 40 percent.

"While past studies from our group have shown that bacteria travel from the gut to the pancreas, our new study is the first to confirm that fungi too make that trip, and that related fungal population changes promote tumor inception and growth," says senior study co-author George Miller, MD, co-leader of the Tumor Immunology Research Program at Perlmutter Cancer Center at NYU Langone Health. While viruses, bacteria and parasites are recognized by the American Cancer Society as causal factors in the disease, say the study authors, no previous study had linked fungi to pancreatic cancer.

**Study Details**

To determine whether the mycobiome is reprogrammed as normal cells become cancerous (oncogenesis), the team performed analyses over 30 weeks of fecal samples from mice with and without pancreatic cancer. Researchers used genomic and statistical techniques to identify and count the fungal species present. They also attached glowing proteins to fungi to track their migrations through the gut and pancreas.

By the end of study period, the researchers observed significant differences in the size and composition of the fungal population in the cancerous pancreas when compared to the healthy organ. The largest population increase in both mice and in human tissues was seen in the genus *Malassezia*, which includes 14 species. The team also detected abnormally higher numbers in the genera *Parastagonospora*, *Saccharomyces*, and *Septoriella*.

"We have long known that *Malassezia* fungi -- generally found on the skin and scalp-- are responsible for dandruff and some forms of eczema, but recent studies have also linked them to skin and colorectal cancer," says senior co-author Deepak Saxena, PhD, professor of Basic Science and Craniofacial Biology at NYU College of Dentistry. "Our new findings add evidence that *Malassezia* is abundant in pancreatic tumors as well."

To test the effect of changing fungal populations on cancer growth, the team treated the mice with amphotericin B, a strong, wide-spectrum antifungal drug. Along with reducing tumor weight, antifungal treatment also reduced the occurrence of ductal dysplasia, an early cellular step toward pancreatic cancer, by 20 to 30 percent.

"Fungal ablation also strengthened the anti-cancer effect of a standard chemotherapy, gemcitabine, by 15 to 25 percent," says co-first author Berk Aykut, MD, a postdoctoral fellow in Miller's lab.

After the pancreases of the mice had been mostly cleared of fungi by drug treatment, the team then examined the effect on cancer growth if only certain species were allowed to repopulate the organ. They found that cancer grew 20 percent faster in the pancreases of

mice repopulated with *Malassezia* - but not in the presence of other oft-occurring fungal species.

The study results argue that fungi increase cancer risk by activating an ancient, first-responder part of the immune system, the complement cascade. Such mechanisms fight infections, but also trigger the healing process (cell growth) as infections wane. Along these lines, complement has been shown by past studies to encourage aggressive tissue growth (cancer) when combined with genetic flaws.

"Moving forward, one goal for our team is to determine which species are most relevant to cancer, as doing so could guide future attempts to slow tumor growth with targeted antifungal medications, and to avert side effects," says co-first author Smruti Pushalkar, PhD, a research scientist at NYU College of Dentistry.

*Along with Miller and Aykut, study authors from the Arthur Localio Laboratory in the departments of Surgery and Cell Biology at NYU School of Medicine were Ruonan Chen, Jacqueline Kim, Sorin Shadaloey, Pamela Preiss, Raquel Abengozar, Joshua Leinwand, Emma Kurz, Brian Diskin, Dongling Wu, and Juan Kochen Rossi; as well as Narendra Verma in the Department of Medicine. Along with Saxena and Pushalkar, study authors from the Department of Basic Science and Craniofacial Biology at NYU College of Dentistry were Qianhao Li, Xin Li, Yuqi Guo, and Mridula Vardhan; as well as Anjana Saxena in the Biology Department of the Brooklyn College and Biology/Biochemistry Programs of the City University of New York.*

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***http://bit.ly/31NxI0h***

## Novel material with strong action against fungi and tumors was developed

***Researchers have created a composite with antifungal properties that are 32 times greater than those of silver by irradiating a metallic tungstate with electrons and femtosecond laser.***

A new material with antifungal and antitumor properties has been developed by researchers at the Center for Development of Functional Materials (CDMF), one of the Research, Innovation and Dissemination Centers (RIDCs) supported by São Paulo Research Foundation - FAPESP. CDMF is hosted by the Federal University of São Carlos (UFSCar) in São Paulo State, Brazil.

The compound was obtained from a sample of pure silver tungstate (α-Ag2WO4) irradiated with electrons and laser light in pulses lasting a few femtoseconds. A femtosecond is a quadrillionth of a second, the time scale of chemical reactions involving exchanges of electrons between atoms and molecules. The new material is described in an article) published in *Scientific Reports*.

The growing use of semiconductors has unleashed the development of novel materials with a wide range of technological applications. One semiconductor family in particular that has drawn the attention of researchers in materials science is that of ternary tungsten oxides, such as metallic tungstates.

Silver tungstate, which belongs to this family, is an important inorganic material with applications in photocatalysis and photoswitches or as an alternative to conventional wide-band-gap semiconductors. Researchers affiliated with CDMF have been investigating silver tungstate for years.

"In an experiment performed in 2018, in which silver tungstate was irradiated with electrons, we observed under an electron microscope the appearance of tiny 'hairs' that grew on molecules of the material. These were nothing other than filaments of nanoparticles extracted from silver tungstate by electron irradiation," said Elson Longo, Professor Emeritus in UFSCar's Chemistry Department and CDMF's principal investigator.

"Silver is a chemical element with bactericidal properties. Silver tungstate also has these properties, but what we found most striking was that after being modified by electron irradiation and silver filament construction, the composite displayed antifungal activity that was 32 times more effective than before irradiation."

The modified composite's antifungal activity was verified in Candida albicans, the fungus that causes candidiasis and thrush. The researchers cultured the fungus in Petri dishes.

They already knew the minimum amount of silver tungstate required to eliminate the fungus and applied the same quantity of the modified composite to the culture. The result observed was similar.

The researchers then halved the volume of the substance and repeated the procedure, again eliminating the fungus. They repeated the procedure 32 times altogether, always with satisfactory antifungal results, demonstrating that the modified composite's antifungal properties were 32 times more powerful than those of the original silver tungstate.

The composite's antitumor action was tested in mouse bladder cancer cells, which were exposed for 24 hours to different concentrations (4.63 micrograms per milliliter, 11.58 µg/mL, 23.16 µg/mL, and 46.31 µg/mL).

According to Longo, the results showed a significant reduction in cell viability. The best result was obtained with a concentration of 11.58 µg/mL when bladder cancer cell viability fell by 80%.

After they demonstrated the composite's antifungal and antitumor properties, the researchers at CDMF and UFSCar investigated its safety for future use in human patients.

Four concentrations of the irradiated silver tungstate composite that were above the optimal range of fungicidal activity (3.9 µg/mL - 31.2 µg/mL) were studied in a human gingival fibroblast cell line.

After incubation for 24?hours, the composite's effect on cell viability, proliferation and morphology was evaluated by quantitative fluorometric assay and scanning electron microscopy.

"We found no statistically significant loss of cell viability at these concentrations compared to the control, showing that the composite poses no risk to human health," Longo said.

## Wave-particle duality

The study also achieved the important scientific milestone of demonstrating wave-particle duality experimentally. The wave-particle duality is a fundamental property of matter proposed in 1924 by French physicist Louis-Victor de Broglie (1892-1987), according to whom electrons and other discrete bits of matter, until then considered only to be material particles, could also have wave properties, depending on the experiment.

"In 1929, the Nobel Prize in Physics was awarded to de Broglie for the discovery that all matter can have wave properties. In the nine decades since, wave-particle duality has been observed and proven in a large number of scientific experiments, but until now, no one has demonstrated it experimentally using beams of particles [electrons in this case] and beams of waves [laser] to obtain identical alterations in compound materials," Longo said.

"When we realized that electron radiation produced silver nanoparticle filaments on silver tungstate, we decided to investigate whether the same result could be achieved by using laser light, thereby experimentally proving the wave-particle duality proposed by de Broglie 95 years ago."

The scientific literature currently points to the growing use of femtosecond laser radiation in material processing as a technique for obtaining novel compounds with highly attractive properties capable of driving technological advances.

"During the electron irradiation process, structural disorder is introduced into the silver tungstate electrons, and this plays a key role in the nucleation and growth of silver filaments," Longo said.

In principle, segregating silver atoms by femtosecond laser radiation should occur in a similar manner but should theoretically be faster because a femtosecond laser pulse can supply maximum power in a very short amount of time.

"Given the expected segregation speed, therefore, the morphology of these silver nanoparticles would theoretically tend to be different under electron beam and femtosecond laser radiation," Longo said.

The practical results exactly matched the theory. When submitted to femtosecond laser radiation, the surface of the silver tungstate was covered with silver nanoparticle filaments.

"By doing this, we succeeded in obtaining exactly the same result as with electron radiation, demonstrating wave-particle duality in practice," Longo said.

*A paper on this previous CDMF experiment was published in 2018, also in* Scientific Reports. *"We received a congratulatory letter from the journal's editor, saying this paper in particular was one of the 100 most read articles on materials science published in the journal last year."*

***http://bit.ly/2IqE7XM***

## Canadians told to stop taking aspirin to prevent first heart attack, stroke

### *Canadian family physicians warned potential harm of daily dose outweighs benefits*

If you've never had a heart attack or stroke, you likely should not be taking aspirin to prevent them, according to new research.

"This is the most significant practice-changing evidence to come out in the past year," said Michael Kolber, a family medicine professor at the University of Alberta and co-author of a paper published in *Canadian Family Physician*, along with recent University of Calgary family medicine graduate Paul Fritsch.

Kolber and Fritsch reviewed three large, randomized, placebo-controlled studies published in 2018 that showed the risk of major internal bleeding associated with taking an aspirin a day is higher than any preventative benefits.

"These aren't nosebleeds or bleeding gums," Fritsch said. "These are major internal bleeds where the patients need hospitalization and perhaps a blood transfusion, so they're of major clinical, and also personal, significance."

Fritsch said one of the studies also showed an increase in deaths from all causes, and in particular cancer deaths, among the patients who took aspirin, which is also called acetylsalicylic acid or ASA.

The advice to take a daily aspirin to prevent heart disease became dogma in the 1990s but it was based on flawed research, according to Kolber.

In an earlier study, Kolber found that 40 per cent of Albertans over the age of 50 take aspirin to prevent cardiovascular disease, even though most have never had a cardiovascular event. He noted that aspirin is still considered beneficial for those who do have heart disease.

"We really see an aspirin gap," said Kolber. "There are a lot of people taking aspirin for primary prevention who don't need it, and there's a group of people who already have cardiovascular disease who aren't taking it, and they should be."

Kolber advises those who have never had a heart problem to use other preventive measures.

"Instead of just taking a daily aspirin like we've been taught for a generation, we would recommend patients stop smoking, exercise, track their blood pressure and consider the Mediterranean diet."

Kolber said people with elevated future cardiovascular risk might consider taking a statin, which lowers cholesterol.

"The evidence for those measures is far superior to the evidence for aspirin," he said.

Kolber and Fritsch's findings were distributed electronically through Tools for Practice, evidence summaries compiled by the U of A's evidence-based medicine team, PEER (Patients, Experience, Evidence, Research). They are read by 40,000 health-care professionals around the world and funded by the Alberta College of Family Physicians and the Canadian College of Family Physicians.

http://bit.ly/2pM4G33

# Fragmented physical activity linked to greater mortality risk

***Accelerometer measurements of older adults suggest that fragmented physical activity may precede reductions of total activity as a sign of increased mortality***

Although reduced physical activity during the day is widely seen as a harbinger of mortality in older people, fragmentation of physical activity--spreading daily activity across more episodes of brief activity--may be an earlier indicator of mortality risk than total amount of daily activity, according to a new study from scientists at the Johns Hopkins Bloomberg School of Public Health.

The study, to be published October 2 in JAMA Network Open, used physical activity data collected using wearable monitors in 548 well-functioning older adults enrolled in the National Institute on Aging's Baltimore Longitudinal Study of Aging. The scientists found that for this group of people during the period 2007-17 there was no association between overall daily activity levels and greater mortality risk. However, there was an association between mortality risk and more fragmented physical activity.

"Fragmentation of physical activity may be an early indicator of increasing mortality risk," says study lead author Amal Wanigatunga, PhD, assistant scientist in the Bloomberg School's Department of Epidemiology. "By examining these patterns of routine activity and the decline in patterns of fragmented activity, we can begin to identify trajectories toward premature serious illness and death sooner and work to develop interventions and preventive strategies to reverse it."

Adults age 65 and older are one of the fastest growing segments of the U.S. population. They are also increasingly sedentary, and prior studies have shown that less physical activity among older adults is a predictor of more illness and premature death. But in recent years, Wanigatunga, along with study senior author Jennifer Schrack, PhD, associate professor in the Department of Epidemiology at the Bloomberg School, and their colleagues, have begun to explore activity fragmentation as a complementary and potentially more sensitive marker of overall health and functioning among older adults.

For the new study the scientists analyzed data from the ongoing Baltimore Longitudinal Study of Aging (BLSA), the U.S's longest-running study of human aging, which began in 1958 and in recent years has included the use of accelerometers by participants to track both quantities and patterns of daily physical activity. The analysis was based on accelerometer data collected between 2007 and 2015 and subsequent mortality data collected between 2007 and 2017 from 548 BLSA participants aged 65 and older.

Of the 548 participants studied, 487 were alive at the end of 2017, and 61 were deceased. The living participants engaged in an average of 5.7 hours of activity per day, compared to 4.7 hours for those who later died. But after accounting for confounding factors such as age, sex, race, body mass index, and existing illnesses, Wanigatunga and colleagues found that total physical activity overall was too weakly associated with mortality risk to reach statistical significance.

Not so for activity fragmentation. The researchers found that for each 10 percent higher activity fragmentation there was a 49 percent increase in the risk of mortality. The researchers defined activity fragmentation as the probability of transitioning from an active state to a sedentary state for each participant, so shorter average activity periods meant higher fragmentation.

The researchers also analyzed the duration of each participant's bouts of activity, and found that "percent of activity spent in bouts of less than five minutes" appeared to be another good marker of mortality risk. Each additional 10 percent of active time spent in

such short bouts was associated with a 28 percent increase in the chance of mortality. Percent of active time spent in 5- to 10-minute bouts was not a significant indicator of mortality risk.

Percent of active time spent in bouts longer than 10 minutes--such as deliberate physical exercise--also didn't reach statistical significance as a marker of mortality risk, but unsurprisingly showed a trend towards being a marker of reduced mortality risk.

Wanigatunga notes that the BLSA cohort they studied had an average age of 76 but was, on the whole, healthier than the general population of older adults in the U.S.

He notes too that although time spent exercising, such as brisk walking, is often examined as a marker for mortality risk, most physical activity for older adults comes from the ordinary, lighter-intensity activity routinely performed throughout the day, such as doing laundry, preparing meals, gardening, and even getting the mail.

Wanigatunga and Schrack and their colleagues are continuing to study activity fragmentation as a potential indicator of health decline, including cognitive decline and dementia. In principle, older adults could have their activity fragmentation monitored this way with wearable monitoring devices to help maintain a high quality of life and preserve the ability to live independently.

"A doctor seeing a patient transitioning into a more fragmented activity pattern and a more sedentary state might initiate a prescription for a tailored physical activity regimen, hopefully as an effective way to restore normal patterns of activity, rather than just saying 'You need to exercise more!'" Wanigatunga says. "I think that type of clinical application, where we aim to wield exercise formally as medicine, is where the study of activity fragmentation can take us."

*"Association of Total Daily Physical Activity and Fragmented Physical Activity and Mortality in Older Adults" was written by Amal A. Wanigatunga, Junrui Di, Vadim Zipunnikov, Jacek K. Urbanek, Pei-Lun Kuo, Eleanor M. Simonsick, Luigi Ferrucci, and Jennifer A. Schrack.*

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***http://bit.ly/35dXbC7***

## African evidence support Younger Dryas Impact Hypothesis

***First African evidence to support hypothesis of an asteroid impact that contributed to the extinction of large animals 12,800 years ago***

A team of scientists from South Africa has discovered evidence partially supporting a hypothesis that Earth was struck by a meteorite or asteroid 12 800 years ago, leading to global consequences including climate change, and contributing to the extinction of many species of large animals at the time of an episode called the Younger Dryas.

The team, led by Professor Francis Thackeray of the Evolutionary Studies Institute at the University of the Witwatersrand in Johannesburg, South Africa, discovered evidence of a remarkable "platinum spike" at a site called Wonderkrater in the Limpopo Province, north of Pretoria in South Africa. Working with researcher Philip Pieterse from the University of Johannesburg and Professor Louis Scott of the University of the Free State, Thackeray discovered this evidence from a core drilled in a peat deposit, notably in a sample about 12 800 years old. This research was published in *Palaeontologia Africana*.

Noting that meteorites are rich in platinum, Thackeray said "Our finding at least partially supports the highly controversial Younger Dryas Impact Hypothesis (YDIH). We seriously need to explore the view that an asteroid impact somewhere on earth may have caused climate change on a global scale, and contributed to some extent to

the process of extinctions of large animals at the end of the Pleistocene, after the last ice age."

Many mammals became extinct in North America, South America and Europe at the time of the Younger Dryas. In South Africa a few extraordinary large animal species became extinct, not necessarily at exactly 12 800 years ago, but close to that period. These megafauna include a giant African buffalo, a large zebra, and a very big wildebeest.

Human populations may also have been indirectly affected at the time in question. In North America there is a dramatic termination of the stone tool technology of Clovis people. Remarkably, archaeologists in South Africa have detected an almost simultaneous termination of the Robberg stone artefact industry associated with people in some parts of the country, including the area around Boomplaas near the Cango Caves in the southern Cape, close to the town of Oudshoorn.

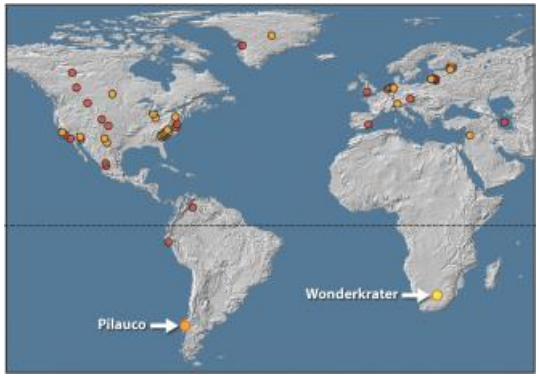
"Without necessarily arguing for a single causal factor on a global scale, we cautiously hint at the possibility that these technological changes, in North America and on the African subcontinent at about the same time, might have been associated indirectly with an asteroid impact with major global consequences," says Thackeray. "We cannot be certain, but a cosmic impact could have affected humans as a result of local changes in environment and the availability of food resources, associated with sudden climate change."

At Wonderkrater, the team has evidence from pollen to show that about 12 800 years ago there was temporary cooling, associated with the "Younger Dryas" drop in temperature that is well documented in the northern hemisphere, and now also in South Africa. According to some scientists, this cooling in widespread areas could at least potentially have been associated with the global dispersal of platinum-rich atmospheric dust.

A large crater 31 kilometres in diameter has been discovered in northern Greenland beneath the Hiawatha Glacier. "There is some evidence to support the view that it might possibly have been the very place where a large meteorite struck the planet earth 12 800 years ago," says Thackeray. "If this was indeed the case, there must have been global consequences."

Thackeray's team believes their discovery of a platinum spike at about 12 800 years ago at Wonderkrater is just part of the strengthening view that an asteroid or cometary impact might have occurred at that time.

This is the first evidence in Africa for a platinum spike preceding climate change. Younger Dryas spikes in platinum have also been found in Greenland, Eurasia, North America, Mexico and recently also at Pilauco in Chile. Wonderkrater is the 30th site in the world for such evidence.




***This is a world map that shows where similary platinum spikes have been discovered in the world. The latest discovery is at the Wonderkrater site in Limpopo Province, South Africa.*** **Francis Thackeray/Wits University**

"Our evidence is entirely consistent with the Younger Dryas Impact Hypothesis" says Thackeray.

The discovery in South Africa is expected to be integrated with those made in other parts of the world, recognising that the source of the platinum at Wonderkrater could hypothetically be cosmic dust that was dispersed in the atmosphere after a meteorite impact in Greenland.

The probability of a large asteroid striking Earth in the future may seem to be low, but there are thousands of large rocks distributed

primarily between Jupiter and Mars. One in particular, classified as Apophis 99942, is referred to as a "Potentially Hazardous Asteroid". It is 340 meters wide and will come exceptionally close to the Earth in 10 years' time.

"The closest encounter will take place precisely on Friday April 13, 2029," says Thackeray. "The probability of the Apophis 99942 asteroid hitting us then is only one in 100 000, but the probability of an impact may be even higher at some time in the future, as it comes close to Earth every 10 years."

*The South African research has been supported by the National Research Foundation and the DST/NRF Centre of Excellence for the Palaeosciences.*

**http://bit.ly/2Iq2aWG**

## Ancient genomes provide insight into the genetic history of the second plague pandemic

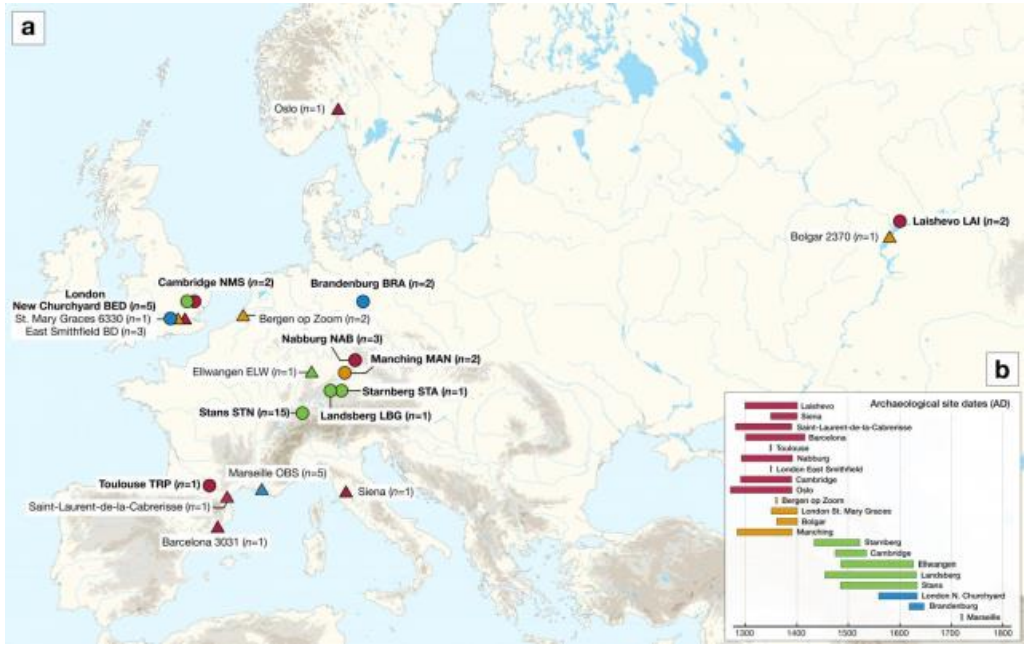
***Analysis of 34 ancient plague genomes from the Black Death and succeeding plague epidemics in Europe between the 14th and 17th centuries, reveals how the bacterium diversified after a single introduction***

An international team of researchers has analyzed remains from ten archaeological sites in England, France, Germany, Russia, and Switzerland to gain insight into the different stages of the second plague pandemic (14th-18th centuries) and the genetic diversity of *Yersinia pestis* during and after the Black Death. In a study published in Nature Communications, the researchers reconstructed 34 *Y. pestis* genomes, tracing the genetic history of the bacterium, which revealed key insights into the initiation and progression of the second plague pandemic in Europe.

The second plague pandemic, which began with the Black Death in the mid-14th century and continued with devastating outbreaks in Europe and the vicinity until the 18th century, decimated the continent, causing the death of up to 60% of the population. But where did this strain of *Yersinia pestis*, the plague causing bacterium, come from? And how did it evolve and expand once it arrived?

**A likely point of entry for *Y. pestis* during the second pandemic**

Despite the ubiquity of the Black Death in historical texts and the popular imagination, the entry point of the *Y. pestis* bacterium at this time and the route it traveled through Europe remain unclear, due to a lack of data from early outbreaks and a general scarcity of published ancient *Y. pestis* genomes.




***Locations of newly sequenced (circles) and previously published (triangles) plague genomes, colored by their temporal order.*** **Spyrou et al.: Phylogeography of the second plague pandemic revealed through analysis of historical Yersinia pestis genomes, *Nature Communications*, DOI: 10.1038/s41467-019-12154-0 (Figure 1)**

In the current study, researchers reconstructed plague genomes from the teeth of 34 individuals, including two from Laishevo, in the Volga region of Russia, and found a single strain that is ancestral to all second pandemic strains. In addition, the researchers

observe an absence of genomic diversity from samples during the Black Death. "These findings indicate a single entry of *Y. pestis* into Europe through the east", explains first author Maria Spyrou of the Max Planck Institute for the Science of Human History. "However, it is possible that additional interpretations may be revealed with future discoveries of un-sampled diversity in western Eurasia", she notes.

**Persistence of *Y. pestis* within Europe**

Although the researchers found that the European-wide Black Death was likely caused by a single strain, analysis of genomes from later in the pandemic shows the emergence of a lineage displaying a higher genetic diversity.

"In the later phase of the second pandemic, we see the development of multiple branches within Europe, which suggests that plague was maintained in different local foci", says Marcel Keller, co-first author of the Max Planck Institute for the Science of Human History. "No modern descendants of this lineage have been found to date, possibly indicating the extinction of these reservoirs."

The researchers also identified a deletion including two virulence-related genes from genomes within this second lineage. Interestingly, genomes from the late stages of the first plague pandemic have shown a deletion in the same region.

"Given that this deletion occurred in lineages from the first and second pandemic, both now extinct, determining how these genes impact maintenance in human and flea hosts would be an important area for future study", comments Kirsten Bos, research group leader of the Max Planck Institute for the Science of Human History.

The current study provides new perspectives into the initiation and progression of the second plague pandemic and adds significantly to the database of published ancient *Y. pestis* genomes.

"We have shown that extensive analysis of ancient *Y. pestis* genomes can provide unique insights into the microevolution of a pathogen over a period of several hundred years", says senior author Johannes Krause, Director of the Department of Archaeogenetics at the Max Planck Institute for the Science of Human History. In the future, integrating this data into disease modelling efforts, in conjunction with data from other areas such as climate science, epidemiology and history, will be important for better understanding the second plague pandemic.

***http://bit.ly/2OoDOk4***

**The Scientific Evidence for the Health Benefits of Cordyceps**

***The cordyceps fungus is said to have the power to fix a host of health problems from muscle fatigue to diabetes. But are the claims too good to be true?***

**By Sabrina Stierwalt, PhD,**

**Listen**

A stronger immune system, more energy, improved endurance, and better stamina … one ingredient promises all of that. Whether it's as an extract, a pill, or powdered into your coffee, the cordyceps fungus is promoted as a one-stop-shop to cure what ails you. Known as Himalayan Gold because it is often farmed in the Himalayan plateaus, cordyceps has long been used in ancient Chinese and Tibetan medicine for curing diarrhea, headache, cough, rheumatism, liver disease, kidney disease, and much more. But is it too good to be true?

**What is Cordyceps?**

As we discussed in a previous episode, the cordyceps fungus grows like a parasite out of the brains of insects and spiders. The fungus takes over the bodies and brains of its victims forcing their zombified bodies to permanently relocate to the trees and low-lying jungle plants where the conditions are ideal for the fungus to thrive.

There are around 400 different species of cordyceps and many different biologically active compounds, but those most commonly used in medicine tend to be cordyceps sinesis and cordyceps

militaris. A jar of 90 capsules will run you around $20, but if you want your dose straight from the source, a single dried wild Himalyana cordyceps sinsensis can cost $10 or more.

**Cordyceps May Fight Muscle Fatigue**

The species cordyceps militaris has been found to have anti-fatigue effects in mice. In one study, mice were given forced swimming and forced running tests. The mice treated with cordyceps had increased ATP levels. (ATP, which stands for adenosine triphosphate, is a chemical that provides energy to our cells for things like muscle contraction.) The treated mice also had lower levels of lactic acid relative to untreated mice. But more research is needed to understand whether humans would see similar results.

Multiple studies involving average, non-athletes have shown a slight increase in VO2 max for participants taking cordyceps sinesis and cordyceps miliatris supplements over those taking a placebo pill. A person's VO2 max is a measure of how fast the body delivers oxygen to the muscles so that the muscles can use that oxygen to produce energy. Elite runners, for example, have almost double the VO2 max of an average person.

**Cordyceps May Have an Antiaging Effect**

Again, research in this area used mice rather than humans. In mice tested for learning and memory, studies have shown that taking extracts of cordyceps sinesis and cordyceps militaris improved brain function. It also boosted antioxidative enzyme activity which helps combat the cell damage that generally comes with age. The same extract was found to improve the sexual function in castrated rats and gives you an idea of how the fungus also gets the nickname "Himalayan Viagra."

**Cordyceps May Help with the Management of Type 2 Diabetes**

For diabetics, the body has trouble making or using insulin, which results in excess sugar in the blood. That excess blood sugar can cause significant health problems. So, those with diabetes have to carefully monitor their blood sugar levels, often with the help of additional insulin. Several studies—again, in mice—have shown that taking cordyceps supplements effectively plays the role of that extra insulin shot by mimicking insulin to the decrease the blood sugar levels. Some of the rats even showed signs of improved kidney function, an issue that often accompanies diabetes.

**Cordyceps May Help Boost the Immune System**

In studies of cell cultures—think cells in dishes rather than in bodies—cordyceps extracts have been shown to increase proinflammatory cytokines. These molecules are excreted from immune cells like T cells and macrophages to regulate inflammatory reactions, which in turn aids in boosting the immune system. The potential revealed by these studies not only suggests an ability to combat an existing disease, but also to enhance the body's innate ability to resist new diseases.

Because most of the clinical studies on the health benefits of cordyceps focused on mice and rats, whether or not these benefits extend to humans remains a big question mark. But centuries of Chinese medicine, as well as recent anecdotal evidence, strongly suggest there is a lot of potential in these fungal stalks. The small number of human-based studies that exist are promising. As is true for other types of natural medicines that have been used over many years without clinical trials to back them up (like breastmilk), just because concrete evidence does not yet exist doesn't mean it's not out there.

Eating a zombie ant fungus for better health may sound bizarre, but using a fungus to fix us is not *that* unusual. After all, we rely on penicillin, which is derived from the fungal species penicillium, as a powerful antibiotic. There is also growing clinical evidence that cordyceps may have the potential to assist in drug development for fighting things like tuberculosis and even cancer cells.

If you are looking to feel less tired or have more energy, adding a little mushroom to your coffee probably won't hurt. They boast their own nutritional value as they are rich in amino acids, and vitamins like B1, B2, B12, and K. As with all forms of medical treatment, if you're looking to address something more serious, its best to consult with a physician.

***http://bit.ly/31TmUOp***

## Vaping-linked lung illness looks like exposure to mustard gas, doctors say

***The outbreak of vaping illnesses is "continuing at a brisk pace," CDC official says.***

**Beth Mole - 10/4/2019, 6:56 AM**

Close examination of lung tissue from 17 people with severe vaping-linked injuries found a type of tissue damage seen in people exposed to toxic fumes and chemical weapons, such as mustard gas. That's according to a short report in The New England Journal of Medicine published Wednesday by doctors from the Mayo Clinic.

It's still unclear what's causing a rash of life-threatening lung injuries in some people who vape. As of October 1, there have been 1,080 confirmed or probable cases in 48 states and the US Virgin Islands, including 18 deaths in 15 states, according to the Centers for Disease Control and Prevention.

Investigators are focusing on contaminants and counterfeit vaping products, particularly those containing THC, the primary psychoactive ingredient in marijuana. Nearly 80% of 578 patients that the CDC has detailed data on reported using THC-containing vaping products in the months before falling ill. Some of the products that have come up in the investigations include Dank Vapes, Moon Rocks, Off White, and TKO, according to The New York Times.

The outbreak is "continuing at a brisk pace," Dr. Anne Schuchat, CDC's principal deputy director, said in a conference call with reporters Thursday.

Amid the fast-moving public health issue, doctors are trying to hone their understanding of the clinical and pathological features of the illnesses. The short report in the NEJM Wednesday adds to that understanding. In all the cases, pathologists found acute tissue injury, inflammation and congestion in the small airways, and "foamy" immune cells.

All of this looks like the telltale signs of exposure to toxic chemical fumes or chemical weapons, such as mustard gas, Dr. Brandon Larsen told the Times. Larsen is a surgical pathologist at the Mayo Clinic in Scottsdale, Arizona and an author on the NEJM report.

"To be honest, they look like the kind of change you would expect to see in an unfortunate worker in an industrial accident where a big barrel of toxic chemicals spills, and that person is exposed to toxic fumes, and there is a chemical burn in the airways," he said.

In such cases, cells in the lungs and airway lining die off. That cell death triggers immune responses that lead to swelling, the sloughing off of the dead cells, and fluids leaking into the lungs. All of those things in turn make breathing difficult if not impossible, he explained.

Of the 17 patients involved in the pathology study, two died from their lung injuries. Doctors aren't sure about the long-term recovery or consequences for the survivors.

"Based on the severity of injury we see, at least in some of these cases, I wouldn't be surprised if we wind up with people down the road having chronic respiratory problems from this," Dr. Larsen said.

In the meantime, investigators continue to try to identify the cause of the illnesses. Notably, the pathology results of the 17 patients' samples showed no signs of lung tissue clogged by oils, such as

vitamin E acetate. The supplement had been found in some suspect products linked to lung injury cases, and some researchers had speculated that such oily cutting agents in vaping liquids could be the culprits behind the injuries. Researchers and investigators at the CDC say more than one ingredient or toxic contaminant could be causing the injuries.

***http://bit.ly/2oVyudc***

## Sixth in a line of Alzheimer's drugs fails in trials

***Treatments designed to stop amyloid peptide formation seem to cause cognitive impairment rather than prevent it***

**By Sarah Houlton4 October 2019**

In yet another setback for Alzheimer's research, Biogen and Eisai have halted two Phase III clinical trials on the BACE (beta-amyloid cleaving enzyme, or beta-secretase 1) inhibitor elenbecestat in early-stage disease. It is the sixth BACE inhibitor to enter clinical trials only to fail.

'While there are differences in terms of toxicity among the different drugs, it appears there is a class effect that high-dose BACE inhibition causes cognitive worsening, the opposite of what we are trying to do,' says Paul Aisen, director of the Alzheimer's Therapeutic Research Institute at the University of Southern California.

BACE is one of the enzymes responsible for cleaving the plaque-forming amyloid-beta peptide from amyloid precursor protein (APP). Inhibiting BACE or another APP-cleaving enzyme, gamma secretase, should stop amyloid beta production before it can agglomerate into plaques in the brain and cause inflammation.

Aisen does not believe that this is the end for BACE inhibition, however. It may be that the drugs are simply too effective at inhibiting the enzyme, causing the toxic side-effects. 'The evidence to date suggests that a 70–90% inhibition of the enzyme is too much,' he says. 'It is intolerable and interferes with cognitive function.'

He remains optimistic that it could be possible to find a dosing strategy that is both effective and well tolerated. 'I believe that dosing strategy will aim for 30–50% inhibition of the enzyme,' he says. This optimism is based on analysis of trial data that suggest that the higher the dose, the worse the cognitive impairment.

BACE inhibition is not the only mechanism targeting amyloid to prove unsuccessful in the clinic – gamma-secretase inhibitors have failed, too, including Lilly's semagacestat and avagacestat from Bristol-Myers Squibb. Gamma-secretase, like BACE, has multiple substrates in the body, and blocking it can stop its other actions, as well as its activity on APP.

Rudolph Tanzi, director of the Genetics and Aging Research Unit at Massachusetts General Hospital in Boston, is not optimistic that either BACE or gamma-secretase inhibition will succeed. He suggests the answer might lie in modulating gamma-secretase, rather than blocking it. As well as early studies using non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, which proved insufficiently powerful, more recently Tanzi has been developing non-NSAID gamma-secretase modulators with the US National Institutes of Health's Blueprint Neurotherapeutics Network. They hope to start Phase I trials in the near future.

'I'm betting on gamma-secretase modulators because then gamma-secretase will still hit all its other substrates,' Tanzi says. However, he says, it will be important to use it in people who are pre-symptomatic. 'Once a patient is showing diagnosis, even the earliest stage of mild cognitive impairment, in my opinion that is too late. You really have to hit the brain before it is damaged.'

He compares amyloid plaques to matches, and the tau tangles they form to brush fires, both of which the brain can live with. 'But once you trigger the forest fire of neuroinflammation, you kill 10–100

times more neurons than plaques and tangles kill,' he says. 'That's when you start showing symptoms, and it's too late to blow out the match or stomp out the brush fires.

'I am very optimistic that if we can safely hit neuroinflammation, you will put out the fire, and never underestimate the ability of the forest to grow back. If you stop neuroinflammation, the brain has the chance to recover. We might stabilise, or even improve, Alzheimer's patients if we can stop neuroinflammation safely.'

Several companies are looking to address neuroinflammation. The furthest advanced, AZTherapies (Tanzi chairs its scientific advisory board), has a drug in Phase III targeting the gene CD33, which turns microglial cells in the brain into killer cells. Inhibiting this gene could prevent neuroinflammation, and the first data from the trial is due next year. The opposite tack would be to activate another gene, TREM2, which is the 'off' switch for this mechanism. AbbVie and Alector are collaborating on projects targeting TREM2 and CD33, both of which are in Phase I. An alternative approach is being taken by Denali in collaboration with Sanofi, targeting a different protein, RIPK1 (receptor-interacting serine/threonine-protein kinase 1), a signalling protein involved in the tumour necrosis factor receptor pathway. This is also in Phase I.

Results of numerous other Alzheimer's trials are expected in the next three or four years. These include Eisai–Biogen's BAN2401, an antibody that prevents amyloid deposition in mouse models, and Aisen is involved in a trial in collaboration with Lilly using an anti-amyloid antibody in clinically normal people, from which early data is due towards the end of 2022.

There is cause for optimism among all the trial failures, Aisen says, not least because of advances in positron emission tomography imaging that allow amyloid and tau levels to be monitored in the brain, and also the ability to measure amyloid peptides in the blood. 'This gives us a ready tool for monitoring people at any stage, including in a primary prevention approach,' he says. 'We also now have tools for monitoring the degree of neurodegeneration with blood tests, we have better clinical trial designs, and we are collaborating and sharing data more effectively. There are many advances that should give us cause for optimism, even in the face of all the frustrating failures.'

But even if a drug can be found, it will need to be dosed in the long term. 'Any drug for maintaining amyloid levels would have to be taken for decades, the same way people take [statins] for cholesterol,' Tanzi says. 'Amyloid is still a great target – the genetics guarantee that – but you have to hit it five, 10, 15, even 20 years before the symptoms appear. It's too late once you're symptomatic.'

***http://bit.ly/2Mq93su***

## Study: Aggressive breast cancers store large amounts of energy, which enables it to spread

***The finding suggests a potential target in the metabolism that could slow or prevent breast cancer metastasis***

ANN ARBOR, Michigan -- Cancer cells - especially the more aggressive ones - seem to have an ability to change. It's how they evade treatment and spread throughout the body.

But how does a cancer cell get the energy it needs to do this?

"We wondered if a cancer cell that wants to change its function can redirect energy not because it takes on new energy but because it has a stored reservoir of potential energy," says Sofia D. Merajver, M.D., Ph.D., professor of internal medicine and epidemiology at the University of Michigan and a researcher at the University of Michigan Rogel Cancer Center.

Merajver's lab looked at levels of glycogen, which represents a stored collection of glucose molecules. Glucose converts to energy, which cancer uses to grow, spread and metastasize.

The team measured glycogen levels in cell lines representing triple-negative breast cancer, inflammatory breast cancer, hormone receptor positive breast cancer and normal breast cells.

The study, published in PLOS ONE, found that aggressive cancers stored glycogen in very large amounts, depending on available oxygen. It's on the order of what's stored in the liver - an organ whose key function is storing glycogen.

"It was surprising just how much glycogen these cancer cells were storing," Merajver says. "This means the cancer has that whole amount of glycogen ready to break down into glucose molecules when the need arises." Even more surprising, the researchers found that an enzyme controlling glycogen degradation in the brain played a key role in glycogen control in breast cancer. The enzyme PYG exists in several forms, including brain and liver. PYGB is primarily expressed in the brain.

Researchers knocked down PYGB in breast cancer cells and found the cells could not use these energy stores and became much less aggressive. They did not see the same effect in the normal breast cells.

"This is a completely new way to look at the plasticity of breast cancer cells," Merajver says. "We think that this ability to change, for breast cancer cells to rewire themselves depending on their environment, is why many patients become resistant to precision medicines. Our study shows one way the cancer cells do this is by creating a reservoir of building blocks or energy."

Researchers believe PYGB could be a potential target to treat or prevent breast cancer metastases. Further studies will explore this link in animal models. Researchers will also investigate whether glycogen phosphorylases inhibitors, which have been studied in diabetes and heart disease, might slow or stop cancer metastasis.

*Additional authors: Megan A. Altemus, Laura E. Good, Andrew C. Little, Joel A. Yates, Hannah G. Cheriyan, Zhi Fen Wu*

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***http://bit.ly/30U9nVi***

## The 'Goldilocks' principle for curing brain cancer

### *U of M Medical School researchers combine ultrasound with engineered glass particles to boost the effectiveness of immunotherapy to combat brain cancer*

MINNEAPOLIS, MN - In the story of Goldilocks, a little girl tastes three different bowls of porridge to find which is not too hot, not too cold, but just the right temperature. In a study published in *Advanced Therapeutics*, University of Minnesota Medical School researchers report on a "Goldilocks" balance which holds the key to awakening the body's immune response to fight off brain cancer.

The most common form of adult brain cancer is glioblastoma. Doctors diagnose about 14,000 glioblastoma cases in the U.S. each year. This aggressive cancer has claimed the lives of Senators John McCain and Edward Kennedy.

"Our body has armies of white blood cells that help us fight off bacteria, viruses and cancer cells. This constellation of cells constitute our immune system," said senior author Clark C. Chen, MD, PhD, Lyle French Chair in Neurosurgery and Head of the Department of Neurosurgery at the University of Minnesota Medical School. "One of the key reasons why glioblastoma is so aggressive is that it shuts off this immune system."

The importance of the immune system in cancer therapy is highlighted by the 2018 Nobel Prize in Physiology or Medicine. The prize was awarded to the discovery of a drug that activates the patient's immune response against cancer cells. Treatment with this immunotherapy drug has produced impressive long-term survival in

many cancer types. Unfortunately, this drug does not appear to work against glioblastomas.

"Immunotherapy works by activating the white blood cells that are present in many cancer types. For reasons that are not clear, glioblastomas contain few white blood cells. So, there is nothing for immunotherapy to activate," commented Andrew Kummel, Professor of Chemistry and Biochemistry at the University of California San Diego and co-senior author of this study.

The research team injected hollowed silica (a form of glass) particles into glioblastomas to facilitate recruitment of white blood cells. The injected tumors were then treated with high-intensity focused ultrasound (HIFU). The ultrasound effectively "blew up" the glass particles to rupture cancer cells, releasing proteins that attract white blood cells.

By modulating the high-frequency ultrasound, Chen and his team were able to create different temperatures under which the cancer cells were ruptured.

"Impressively, immunotherapy works only when the ultrasound is adjusted to maintain a stable body temperature as the cancer cells are ruptured," said Chen. "Temperatures that deviate too much from the body temperature appear to compromise the effectiveness of the white blood cells. This 'Goldilocks' aspect of immunotherapy was not previously appreciated."

Importantly, Emad Ebbini, U of M Professor of Electrical and Computer Engineering, has developed an ultrasound system capable of rupturing cancer cells without the use of the silica shell. Ebbini notes, "Our ultrasound is a perfect fit for the type of clinical application that Dr. Chen has developed. We are working toward a first-in-human study to test our ultrasound in glioblastoma patients."

*Co-authors of this study include Chin-Hsin Huang, and Siamak Amifakhri, University of California San Diego as well as Oscar Echaegaray, San Diego State University. This research was supported by the National Cancer Institute of the National Institutes of Health (T32 Training grant no. 5T32CA153915-08; U54 supplementary grant no. 5U54CA132379-08; 1RON1NS097649-01; 9R44GM128223-02) and funds from the Burroughs Wellcome Fund, the Doris Duke Charitable Foundation, the Sontag Foundation and the Kimmel Foundation.*

***http://bit.ly/2ARct1K***

## Chinese activists protest the use of traditional treatments -- they want medical science

### *Activists are defending modern medical science and criticising Traditional Chinese Medicine*

In the West, the number of people challenging scientific authority has been growing in past decades. This has, among other things, led to a decline in the support for mass vaccination programmes and to an increase in alternative forms of treatment. In China, however, activists are defending modern medical science and criticising Traditional Chinese Medicine, which hospitals are obliged to offer to patients on an equal footing with modern medical care.

Over a number of years, Chinese researcher Qiaoyan Zhu, who has been affiliated with the University of Copenhagen's Department of Communication, has collected data on the many thousand science activists in China through observations in Internet forums, on social media and during physical meetings. She has also interviewed hundreds of activists.

Together with Professor Maja Horst, who has specialised in research communication, Zhu has analysed the many data on the activists and their protests in an article that has just been published in the journal Public Understanding of Science:

"The activists are better educated and wealthier than the average Chinese population, and a large majority of them keep up-to-date with scientific developments. The protests do not reflect a broad popular movement, but the activists make an impact with their communication at several different levels," Maja Horst explained and added:

"Many of them are protesting individually by writing directly to family, friends and colleagues who have been treated with - and in some cases taken ill from - Traditional Chinese Medicine. Some have also hung posters in hospitals and other official institutions to draw attention to the dangers of traditional treatments. But most of the activism takes place online, on social media and blogs.

**The activists hold the cards**

Activists operating in a regime like the Chinese are obviously not given the same leeway as activists in an open democratic society - there are limits to what the authorities are willing to accept in the public sphere in particular. However, there is still ample opportunity to organise and plan actions online.

"In addition to smaller groups and individual activists that have profiles on social media, larger online groups are also being formed, in some cases gaining a high degree of visibility. The card game with 52 criticisms about Traditional Chinese Medicine that a group of activists produced in 37,000 copies and distributed to family, friends and local poker clubs is a good example. Poker is a highly popular pastime in rural China so the critical deck of cards is a creative way of reaching a large audience," Maja Horst said.

Maja Horst and Qiaoyan Zhu have also found examples of more direct action methods, where local activist groups contact school authorities to complain that traditional Chinese medicine is part of the syllabus in schools. Or that activists help patients refuse treatment if they are offered treatment with Traditional Chinese Medicine.

Will we see similar science activism in Europe?

The Chinese style of science activism, which Maja Horst and Qiaoyan Zhu have studied, is rather traditional and fact-based compared to the often more spectacular and symbol-laden communication that Western activists use when, for example, protesting genetic research. But they conclude by anticipating a possible similar development in the West:

"We have already seen Marches for Science in the US and Europe so it is not unlikely we will begin to see more activism in favour of science and evidence-based medicine in our part of the world as well. We may well see a counter-reaction towards climate sceptics and anti-vaxxers who challenge established science and its results."

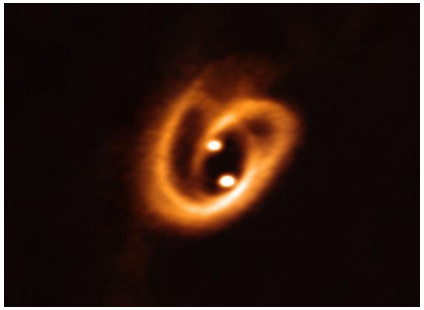
*Read the article "Science Communication Activism: protesting traditional Chinese Medicine in China" in the journal Public Understanding of Science.*

***http://bit.ly/2LRmSB4***

## Double Protostar Caught in Process of Forming

***Astronomers using the Atacama Large Millimeter/submillimeter Array (ALMA) have captured a stunning image of two circumstellar disks in which two protostars are growing, fed by a complex network of filaments of gas and dust.***

Many stars are in binary stellar systems often with the two components having similar masses. It remains unclear how these systems assemble and accrete material.



***This ALMA image shows the binary protostar [BHB2007] 11.*** **Image credit: ALMA / ESO / NAOJ / NRAO / Alves *et al.***

Dr. Felipe Alves of the Max Planck Institute for Extraterrestrial Physics and colleagues used ALMA to conduct the high-resolution observations of [BHB2007] 11, a binary protostar located in the constellation of Ophiuchus, about 700 light-years away.

This system is the youngest member of a small cluster in the Barnard 59 dark nebula, which is part of the clouds of interstellar dust called the Pipe Nebula.

“We see two compact sources that we interpret as circumstellar disks around the two young stars,” Dr. Alves said.

“The size of each of these disks is similar to the asteroid belt in our Solar System and the separation between them is 28 times the distance between the Sun and the Earth.”

The two circumstellar disks in [BHB2007] 11 are surrounded by a bigger disk with a total mass of about 80 Jupiter masses, which displays a complex network of dust structures distributed in spiral shapes.

“This is a really important result,” said co-author Dr. Paola Caselli, also from the Max Planck Institute for Extraterrestrial Physics.

“We have finally imaged the complex structure of young binary stars with their feeding filaments connecting them to the disk in which they were born. This provides important constraints for current models of star formation.”

The protostars in [BHB2007] 11 accrete mass from the bigger disk in two stages.

The first stage is when mass is transferred to the individual circumstellar disks in beautiful twirling loops, which is what the new ALMA image showed.

The data analysis also revealed that the less-massive but brighter circumstellar disk — the one in the lower part of the image — accretes more material. In the second stage, the stars accrete mass from their circumstellar disks.

“We expect this two-level accretion process to drive the dynamics of the binary system during its mass accretion phase,” Dr. Alves said. “While the good agreement of these observations with theory is already very promising, we will need to study more young binary systems in detail to better understand how multiple stars form.”

The study was published in the journal *Science*.

*F.O. Alves* et al. *2019. Gas flow and accretion via spiral streamers and circumstellar disks in a young binary protostar*. Science *366 (6461): 90-93; doi: 10.1126/science.aaw3491*