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Tuberculosis Can Emerge After Cancer Immunotherapy

At least a handful of patients have developed active TB after receiving cancer treatment designed to boost the immune system's antitumor response.

Ashley Yeager

In December 2012, an 80-year-old man in Florida went to his doctor to have a bulge on his eyelid examined. Tests showed that the bump was a rare form of skin cancer called Merkel cell carcinoma. Despite treatment, the man's cancer spread, first to lymph nodes under his jaw, then to lymph nodes in his abdomen. So in June 2015, he enrolled in a clinical trial for Merck's pembrolizumab (Keytruda), a checkpoint inhibitor drug that blocks programmed cell death protein 1 (PD-1) to help the immune system more effectively target and kill tumor cells.

Six months into receiving the experimental treatment, the man developed an odd-looking nodule in his lung that didn't resemble any of his other tumors. Doctors decided to biopsy it. To their surprise, the results came back positive for tuberculosis (TB), though the man didn't have symptoms of a TB infection. In February 2016, he started anti-TB treatment, and fortunately, after a short break from the anticancer treatment, was able to finish the full courses of both therapies in 2017.

Meanwhile, a second patient, an immigrant from Vietnam, where TB is endemic, had enrolled in a trial for Bristol-Myers Squibb's nivolumab (Opdivo), another anti-PD-1 drug progressing through clinical trials. He didn't have such a happy ending: in June 2016, a month after starting the experimental cancer treatment, he developed a tuberculosis infection. A month after that, he died.

"I personally am a little concerned," says Elad Sharon, a medical oncologist at the National Cancer Institute (NCI), which has been one of the government sponsors of clinical trials globally for PD-1 and PD-L1 blockade treatments. Doctors at Emory University, where the Florida man was being treated, alerted the NCI to the man's condition because the agency was responsible for reporting any ill effects of the treatment to the US Food and Drug Administration (FDA). But the man's experience wasn't an isolated case, Sharon says. Reports from other clinical trials of anti-PD-1 treatments also showed tuberculosis infections cropping up in treated patients.

The FDA approved pembrolizumab and nivolumab as therapies for a variety of cancers, starting in 2014. Anti-PD-1 therapies are also being touted as potential treatments for non-cancer diseases such as Alzheimer's. Given the enthusiasm to expand these drugs' use, combined with the fact that the World Health Organization estimates that nearly a quarter of the world's population has latent TB, Sharon's concern seems justified.

"This is something that needs a lot more attention," says Dan Barber, an immunobiologist at the National Institute of Allergy and Infectious Diseases (NIAID) who coauthored with Sharon a study describing the two cases of TB after anti-PD-1 therapy (*Sci Transl Med*, 11:eaat2702, 2019). Those results, and other reports of TB following immunotherapy, suggest that "we should probably be thinking about tuberculosis more during trials and during immunotherapy for cancer and actually see if we can try and get a feel for just how likely this is," he says. "It could be a very rare event or it could be not so rare. . . . It's not clear."

The idea that tuberculosis might emerge after anti-PD-1 isn't a total surprise. In 2010, William Jacobs Jr., a microbiologist at Albert Einstein College of Medicine in New York, and colleagues reported that mice genetically engineered so that they didn't have PD-1 protein surface receptors died extremely quickly compared to healthy mice when infected with the bacterium that causes TB,

Mycobacterium tuberculosis (*PNAS*, 107:13402–407). Essentially, Jacobs says, the study showed that the PD-1 pathway was crucial to controlling inflammation that builds in response to the bacterium. Barber's work as a postdoc at NIAID revealed a similar result: after exposure to *M. tuberculosis* in the air, PD-1 knockout mice developed a lot of *M. tuberculosis*–specific CD4 T cells—which play a role in triggering adaptive immune responses—and those cells actually encouraged the replication of bacteria in the mice (*J Immunol*, 186:1598–607, 2011).

In humans treated for cancer who develop TB, the infections are probably not new, but "the escape of an old infection kept latent thanks to the PD-1 system," says Olivier Lambotte, an infectious disease researcher at Paris XI University Medical School who has described a case of anti-PD-1–emergent TB but was not involved with Sharon's and Barber's work. He explains that PD-1, which is expressed on CD4 T cells, prevents excessive inflammation and immune activation in response to *M. tuberculosis*. With anti-PD-1 therapy, "you release the brakes on T cells . . . so TB disease occurs."

Barber notes that the molecular interactions that lead to illness may be more nuanced. His recent studies in PD-1 knockout mice suggest that CD4 T cells in these animals are making a lot of a cytokine called interferon gamma (*PLOS Pathog*, 12:e1005667, 2016). "Interferon gamma production by CD4 T cells is [the sort of thing] that people think of as being the way the adaptive immune response suppresses tuberculosis," he says. But his work has shown that that's not the case at all. "The outcome of boosting interferon gamma production by T cells in a mouse model of TB is a dead mouse. Not better control of the infection."

Up until the Florida patient presented with TB, there weren't any data on how the human immune system responded to *M. tuberculosis* after anti-PD-1 treatment. Samples taken from the man's blood and analyzed by Sharon's group, however, showed that interferon gamma–producing CD4 T cells specific to *M. tuberculosis* were indeed more abundant after anti-PD-1 treatment. "We were able to really prove, at least to our minds, that the data were consistent with the data that [Barber] had previously put together in the mouse," Sharon says.

Barber, Jacobs, and Lambotte agree that the data suggest that screens for latent TB should be done before a patient undergoes any anti-PD-1 treatment. But Sharon is a bit more hesitant. "We're still thinking about it, in part because I think that we're just not clear on how common this is," he says, especially when it comes to the severe cases of the patients described in last year's *Science Translational Medicine* study. Clinicians and scientists don't usually monitor for TB in clinical trials—and it's possible the nodules that develop from the infection could be mistaken for additional cancer growths.

Still, the results are "definitely telling us something unique about the immune response," Jacobs Jr. says. And, it could lead to innovative treatments for TB, perhaps by using anti-PD-1 treatments to encourage persistent *M. tuberculosis* cells to grow so they can then be killed more quickly by TB drugs—an approach that could help reduce the ability of the bacteria to become latent in the body, he explains. "That's an idea I intend to test."

http://bit.ly/2FUYlbr

Mega study confirms pregnant women can reduce risk of stillbirth by sleeping on their side

Sleeping on the side is better for the baby.

Lesley McCowan* **Robin Cronin****

A New Zealand-led international study published today provides the strongest evidence yet that women can more than halve their risk of stillbirth by going to sleep on either side during the last three months of pregnancy.

This mega study (known as individual participant data meta-analysis) has also confirmed the risk of stillbirth associated with sleeping on the back applies to all pregnant women in the last trimester of pregnancy.

Risk factors

In New Zealand, stillbirth is defined as the loss of a baby after 20 weeks of pregnancy. An estimated 2.64 million babies die before birth globally each year, and around 300 babies are stillborn in Aotearoa New Zealand each year. About one in every 500 women in New Zealand will experience the tragedy of a late stillbirth and lose their baby during or after 28 weeks of pregnancy.

We have analysed all available data worldwide from five previous studies, including our earlier research, the 2011 Auckland Stillbirth Study, which first identified a link between mothers' sleeping position and stillbirth risk. The main finding in the mega study, which included information from 851 bereaved mothers and 2,257 women with ongoing pregnancies, was that going to sleep lying on the back (supine) from 28 weeks of pregnancy increased the risk of stillbirth 2.6 times.

This heightened risk occurred regardless of the other known risk factors for stillbirth. However, the risk is additive, meaning that going to sleep on the back adds to other stillbirth risk factors, for example, a baby who is growing poorly in the womb.

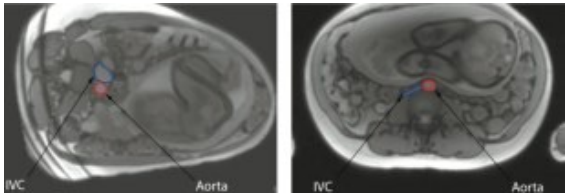
Existing common risk factors for late stillbirth are not easily modifiable. They include advanced maternal age (over 40), obesity, continued cigarette smoking and an unborn baby that is growing poorly, especially if the poor growth is not recognised before birth. Women also have a higher risk during their first pregnancy, or if they have already had three or more babies. Women of Pacific and South Asian ethnicity also have an elevated risk of late stillbirth, compared with European women.

If modifiable risk factors can be identified, some of these baby deaths could be prevented. Importantly, our mega study has shown that if every pregnant woman went to sleep lying on her side after 28 weeks of pregnancy, approximately 6% of late stillbirths could be prevented. This could save the lives of about 153,000 babies each year worldwide.

Reduced blood flow

The relationship between the mother going to sleep lying on her back and stillbirth is biologically plausible. A supine position in late pregnancy is associated with reduced blood flow to the womb. Hence, women in labour and women having a caesarean section are routinely tilted onto their side to improve blood supply to the baby.

Recent research carried out at the University of Auckland has provided sophisticated evidence about how the mothers' position influences blood flow. Results obtained using Magnetic Resonance Imaging (MRI) demonstrate the major vessel in the mother's abdomen, the inferior vena cava, being compressed by the pregnant womb when she is lying on her back. This reduces flow through this vessel by 80%.



The MRI images show the inferior vena cava (IVC) in blue and the aorta in red. In the left image, the mother is lying on her left side, while in the right image, she is on her back. **provided, CC BY-SA**

Although the mother's circulation responds by increasing the flow through other veins, this does not fully compensate. The mother's aorta, the main artery which carries oxygen-rich blood from her heart, is also partly compressed when the mother lies on her back. This decreases blood flow to the pregnant uterus, placenta and baby. We speculate that while healthy unborn babies can compensate for the reduced blood supply, babies that are unwell or vulnerable for

some other reason may not cope. For example, our mega study showed that the risk of stillbirth after 28 weeks of pregnancy is increased approximately 16 times if a mother goes to sleep lying on her back and also is pregnant with a very small baby.

What to do

New Zealand research has shown that pregnant women can change their sleeping position. In a recent survey conducted in pregnant women from south Auckland, a community that has a high rate of stillbirth, more than 80% of women surveyed stated that they could change the position they went to sleep in with little difficulty if it was best for their baby.

Our advice to pregnant women from 28 weeks of pregnancy is to settle to sleep on their side to reduce the risk of stillbirth, and to start every sleep, including day-time naps, on the side. It does not matter which side. It is common to wake up on the back, but we recommend that if this happens, women should simply roll back on to either side.

Professor, Obstetrics & Gynecology, University of Auckland
Midwife researcher, University of Auckland

Disclosure statement
Lesley McCowan receives funding from Cure Kids New Zealand and Red Nose Australia. Robin Cronin received funding from the University of Auckland and the Sir John Logan Campbell Medical Trust during the conduct of the study.

http://bit.ly/2TPAIon

Medicinal plants may be a key to understanding other cultures

A new methodology for comparing herbal medicine across societies can also be used to understand the transfer of cultural traditions.

"I did a thorough documentation of the natural remedies, mostly plants, used by the Amazigh people in the High Atlas. Then, I studied how modernization in its various forms influences the use of plants," explains Irene Teixidor-Toneu, a postdoctoral fellow at the University of Oslo, Norway.

"To summarize, there is a change in the use of substances, since people are open to medication prescribed by the doctor. At the same time, traditional knowledge and beliefs concerning plant use are kept alive, although traditions also change over time."

Having spent almost a year in the Moroccan High Atlas mountains, ethnobotanist Irene Teixidor-Toneu finished her Ph.D. on the use of medicinal plants in Amazigh (Berber) villages.

Her scientific article, describing the methodology, was published in the October issue of the journal *Nature Plants*. She is currently working at the Natural History Museum in Oslo, where her methods will be applied to map the use of medicinal plants in Scandinavia from Viking times until today, in a project that was launched in November 2018.

Modern or traditional medicine?

Her Ph.D. dissertation was devoted to the transmission of knowledge about medicinal plants used by a defined group of people. These were some of the basic questions Teixidor-Toneu studied:

- ***Why are certain plants selected for medical use?***
- ***How are they used?***
- ***How does usage change over time?***

If you were to ask a pharmacist, one obvious explanation to why certain plants are used, is that they contain phytochemicals. Phytochemicals are compounds developed in order help plants thrive or fight competitors, predators, or pathogens. Many phytochemicals have therapeutic effects.

However, there is always a combination of reasons why a plant is selected for use, according to Teixidor-Toneu.

Faith and lore

Ethnobiology is defined as the interdisciplinary study of how human cultures interact with and use their native plants and animals. Ethnobotany is defined as the plant lore of indigenous cultures, also the systematic study of such lore.

Irene Teixidor-Toneu explains: "In studies of plant diversity and conservation, there are a lot of ecological models that don't take people into account at all. If you think of the vegetation in the Mediterranean area, as an example, nothing makes sense if you don't consider humans and their influence. After all, the region has been shaped and developed by man for millennia."

From colouring to food

Most of us probably think of food, spice and medicine, when the subject of plant use is brought up. However, there is a multitude of historic and present practices. Like fumigation.

Fumigation is the physical process of burning and making smoke out of a plant. This can be ritual or medical or a combination of both. It can be done to clean out a dirty room, to remove fleas and ticks and other insects. In Morocco, the Amazigh burn plant that are rich in resins in order to clean the stables for their animals.

Other uses vary from producing and dyeing textiles, making furniture and utensils, construction of houses to providing fodder and veterinary medicine.

The interdisciplinary aspect is one reason why Irene Teixidor-Toneu finds ethnobotany so fascinating:

"There has been a patchwork of approaches and methods because people from different backgrounds have come together, with no common theoretical framework. Researchers from the humanities and natural scientists often have different approaches. In recent years, we have seen some articles trying to unite and define ethnobiology as one discipline, but there are still many ways to regard the interaction of people and plants."

Constructing family trees

Teixidor-Toneu has provided a significant contribution through her perspective article recently published in *Nature Plants*, with co-authors Fiona Jordan (evolutionary anthropologist, University of Bristol) and Julie A. Hawkins (phylogenetist, University of Reading).

Basically, it is a summary of the theoretical analysis for her Ph.D. work. The article proposes a framework to study plant uses. This framework uses phylogenetic comparative methods applied to anthropological data, which involves – to put it simply—the construction of language family trees.

For some time, it has been used by anthropologists to gain understanding of the evolution of political, religious, social and material culture. It has not previously been applied to plant use, as pointed out by the editor of Nature Plants in the editorial:

"Normally we associate the use of (…) phylogenetic analyses to determine the relationships between species and groups of organisms, tracing their evolution back to putative common ancestors. (…) Teixidor-Toneu et al. have applied comparative phylogenetic methods, not to plants themselves but to the medicinal roles to which they have been put. Even within ethnobotany this is not a common approach, but the ability to use multiple types of data can produce robust and detailed information about how cultural information is transmitted"

Medicinal plants are of special interest because of their role in maintaining people's health. Phylogenetic comparative methods can enable researchers to study the diversity of medicinal plant applications across cultures, and also to infer changes in plant use over time.

These methods can be applied to single medicinal plants as well as the entire set of plants used by a culture for medicine, known as a pharmacopoeia.

Plants and cultural knowledge are both endangered

"I think the main significance of our paper is that it opens up new opportunities for studying plant use. At the moment, we are well aware that that biodiversity is threatened. Cultural diversity and traditional lifestyles are also threatened. In other words, many plants as well as the knowledge about how to use them, are endangered. Therefore, there is an urgent need to understand how various threatening factors interact and how use and knowledge change over time," Irene Teixidor-Toneu explains, and adds:

"We are trying to understand plant use across cultures. The first thing we need to understand is how cultures are related. We use phylogeny models, or pedigrees, to trace relationships between people and cultures, based on language similarities."

"Having traced evolutionary relationships between cultures, we can identify and try to understand the ways plants are used in different cultures. Within this framework we can also study how uses change, and it can be linked to geographical models. So, we end up with what we could call a biocultural geography."

https://bbc.in/2WL0mMU

Healthcare: When left-right awareness is crucial

Do you ever struggle to tell your left from your right, maybe when driving or giving directions?

By Catherine Smyth BBC News NI

If so, you're not alone as evidence suggests a significant proportion of the population has difficulties. Usually, it's not a big thing. But, in medicine, adverse events caused by left-right issues can have serious consequences.

A new study from Queen's University Belfast has questioned the idea that determining left from right is effortless for everyone.

It has said that medical education should respond by raising awareness about the challenges some medical students face. In addition to the many checks and balances in healthcare to prevent such errors, the study has also called for greater support to be extended in medical students training.

Mr Ian Walsh is a surgeon and an academic at Queen's.

While re-creating a simple investigation with a group of fourth-year medical students, he illustrates how left and right awareness come into play in everyday situations for medical professionals.

He shows them an X-ray of a set of lungs - the left lung has fluid in it. As viewed straight on, the 2D X-rays appear to flip the left and right sides - in that a student will see the left-hand lung on the right side of the screen.

It's vitally important that the medical students are aware of this and also examine the patient themselves before they proceed to treat the patient by draining the lung.

The new research paper, which is to be published in the journal Medical Education, was led by Prof Gerry Gormley from the Centre for Medical Education at Queens.

It looked at how, for some of us, making left-right decisions is simple - but for others is it's much more problematic.

"In terms of spatial awareness, generally we don't confuse above and below, behind and in front - but left and right can pose a challenge for some people. "It's a relatively under-researched area and still there is a lot to be known about this particular topic. "We know that many individuals can, without thinking, determine the correct side.

"However, for others they have to go through a complex process and use many higher functions to discriminate left from right."

Crucial skill

So this simple skill is actually more complex than it first appears - and it's crucial those in medicine get it right.

Dr Carl Brennan also worked on the research. He said that some students developed their own coping mechanisms.

"One of the most common common ones can be with their hands - where on their left hand they form the 'L' shape.

"There are a number of others - wearing their wristwatch or wedding band on their left side or writing with their right."

Queens University is at the forefront of a field of study called Human Factors.

Simply put, in healthcare, it looks at how professionals best interact and behave with their environment, equipment and other people in the interests of patient safety. It can show medical professionals how best to communicate in teams and effectively handover increasingly complex information to others in healthcare.

Mr Walsh explains its application to left-right issues.

Situational awareness

"This addresses beyond the more technical issues - for example where you mark the right limb to make sure you take off the correct limb, for example. "It looks at improving quality by looking at how we behave, how we think and how we interact."

Prof Gormley said it's important to translate this type of research into practice. "In our future simulation centre, in addition to what we are already doing we can bring students together with drama students, for example.

"They can really re-create challenging situations but also the emotions and the situational awareness so that our medical students can convert their thoughts into correct actions to hopefully reduce error and deliver high quality care."

http://bit.ly/2UcdBsW

Liver, colon cancer cells thwarted by compounds derived from hops

Hops produces a primary compound that thwarts cancer cells

CORVALLIS - The plant that adds flavor, color and bitterness to beer also produces a primary compound that thwarts cancer cells, and two important derivatives of the compound do as well, new research at Oregon State University shows.

Unlike the primary compound, xanthohumol, known as XN, the derivatives don't metabolize into phytoestrogens. Phytoestrogens are plant-based chemicals similar to female sex hormones that help some types of tumors grow and can cause other health problems as well.

The research showed, for the first time, that the derivatives have cancer-fighting effectiveness similar to that of XN in liver and colon carcinomas. That means the two non-estrogenic derivatives are attractive alternatives for testing, along with XN, in future preclinical studies..

The study was published in the International Journal of Molecular Sciences.

Xanthohumol is produced by humulus lupulus, the common hop plant. More than 20 years ago, researchers discovered that XN inhibits cell growth in a variety of cancer cell lines.

"But a potential problem with XN is that enzymes in the liver and the gut microbiota metabolize it into 8- prenylnaringenin, or 8-PN, the most potent phytoestrogen known," said the study's corresponding author, Adrian Gombart, professor of biochemistry and biophysics in the College of Science at Oregon State University and principal investigator at OSU's Linus Pauling Institute.

The derivatives that don't metabolize into 8-PN are DXN, short for dihydroxanthohumol, and TXN, which refers to tetrahydroxanthohumol.

Earlier, Gombart's Linus Pauling Institute colleague and co-author Fred Stevens led a study into DXN and TXN's effects on metabolic syndrome.

"In that previous research we showed that the two derivatives reduced weight gain and improved biomarkers of metabolic syndrome," Gombart said. "XN had been shown to inhibit

proliferation of a variety of cancer cell lines, and in this study, we demonstrated XN's ability to halt cell growth and kill two liver cancer cell lines and two colon cancer cell lines. We tested liver and colon cancer cell lines because oral consumption of XN and its derivatives can lead to high concentrations in the gut and liver."

Colorectal cancer is the third most common cause of cancer-related death in the United States, and liver cancer ranks fifth. The incidence of liver cancer, though, has tripled in the last four decades. "For both of those cancers, discovering new compounds for prevention and treatment is imperative," Gombart said. "In all the cell lines tested, DXN and TXN inhibited cell growth and caused cell death, as did XN. And for most cell types, DXN and TXN were slightly more potent."

Supporting the research were the National Center for Complementary and Integrative Health at the National Institutes of Health; Hopsteiner Inc.; the Buhler-Wang Research Fund; the OSU Department of Biochemistry and Biophysics; and the Linus Pauling Institute.

Collaborating with Gombart were OSU colleagues Stevens, Isabelle Logan, Cristobal Miranda, Malcolm Lowry and Claudia Maier.

http://bit.ly/2Ieqcvh

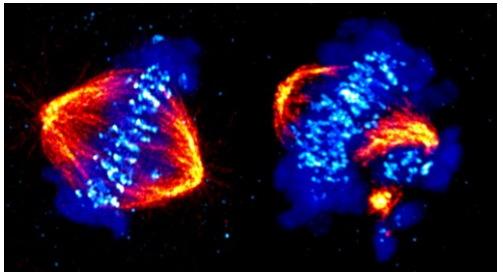
New role for a driver of metastatic cancers

Salk scientists uncover the mechanism of a gene to better target cancer therapy

LA JOLLA - Metastatic ovarian, prostate and breast cancers are notoriously difficult to treat and often deadly. Now, Salk Institute researchers have revealed a new role for the CDK12 protein. The findings were published in the print version of *Genes & Development* on April 1, 2019.

"Approximately 3-5 percent of prostate, ovarian, and breast cancers contain mutations in the CDK12 gene, and recent studies have shown that this subset is uniquely responsive to immunotherapy drugs, whereas the majority of these cancers do not respond," says Salk Professor Katherine Jones, senior author of the paper.

"This suggests, for the majority of these cancers that lack a CDK12 mutation, chemical inhibitors of CDK12 could be used to make the cancer more easily killed by chemotherapy drugs, and potentially more sensitive to immunotherapy treatments as well." The results suggest it could be a drug target for many cancers that have spread throughout the body.



Left: The process of cell division, called mitosis, showing structures called microtubules (orange) pulling the chromosomes (blue) to opposite sides, called spindle poles, of the cell. CDK12 is critical for proper chromosome alignment and progression through mitosis. Right: Without CDK12 the chromosomes become misaligned and detach from the spindle poles. **Credit: Salk Institute**

By analyzing the role of CDK12 in protecting the cells from chemotherapy, the team discovered a new group of genes that are controlled by CDK12, including many genes that are regulated by another protein called mTORC1, which controls cancer cell metabolism. And although CDK12 is predominantly located in the nucleus of the cell, it works with mTORC1 to control the process of translation--an important step in creating a new protein within the cell.

"CDK12 is a recently identified gene that controls the expression of genes required for DNA repair, but its detailed mechanism and function are just beginning to be explored," says first author Seung Choi, a former staff scientist and a current Salk research collaborator. "Therefore, if CDK12 is inhibited, the cell cannot repair DNA efficiently, and the cells are more prone to dying in response to chemotherapy. We wanted to understand how CDK12 might be involved in cancer in order to advance cancer treatment options."

In a collaboration with the lab of Salk Professor Alan Saghatelian, the team was able to identify specific genes that were regulated by CDK12 at the level of translation. Several hundred genes were found to be controlled by CDK12 in this new way, many of which are tied to cancer cell growth.

To the surprise of the researchers, many of the other newly identified CDK12-regulated genes were critical for cell division (mitosis). Microscopy imaging studies by Seunjae Kim, a postdoctoral fellow at Salk, revealed that CDK12 helped the chromosomes condense and then separate to become two distinct cells. This role for CDK12 in the expression of a whole network of genes necessary for mitosis was entirely unknown.

"We've discovered a new translation pathway that nobody knew existed, which is used by a lot of the factors that are involved in cell division--specifically, separating the chromosomes," says Jones, who holds the Edwin K. Hunter Chair in the Regulatory Biology Laboratory.

"This new information about the role of CDK12 helps us understand how cancer cells are disorganized, and also how chemical inhibitors of CDK12 could help kill cancer cells. The findings suggest that targeted inhibitors to CDK12 might also block parts of the mTOR pathway, and synergize with mTOR inhibitors or mitotic inhibitors that are important components of current therapies."

The scientists are now studying how CDK12 is inhibited in normal cells, which could suggest new approaches to blocking CDK12 activity in metastatic cancer cell therapy.

Other authors included Thomas F. Martinez, Seongjae Kim, Cynthia Donaldson, Maxim N. Shokhirev and Alan Saghatelian.

The work was funded by The Jean Hahn Hardy Fellowship, the Salk Alumni Fellowship, the Pioneer Fund Scholar Awards, the National Institutes of Health (NRSA F32GM123685, 5R01HD092215 and R01CA125535).

https://wb.md/2FURldo

What the HPV Vaccine Achieved in Only 6 Years

Brief discussion of a very important paper recently appearing in *Cancer Epidemiology, Biomarkers & Prevention*

Maurie Markman, MD

This transcript has been edited for clarity.

Hello. I'm Dr Maurie Markman from Cancer Treatment Centers of America in Philadelphia. I wanted to briefly discuss a very important paper which recently appeared in *Cancer Epidemiology, Biomarkers & Prevention*, entitled, "Trends in Human Papillomavirus Vaccine Types 16 and 18 in Cervical Precancers, 2008-2014."[1]

The medical community is very aware of the extraordinary effectiveness of HPV vaccination, as data from multiple clinical trials have demonstrated a substantial reduction in the risk for types 16 and 18—the major causes of cervical cancer, as many as 70%-80% of cases worldwide—in the trial setting.

Although one would have predicted that when the vaccine was widely available, the data would show a reduction in the risk for HPV 16/18 in the population, it was important to confirm this result, which was presented in the paper I just mentioned.

This study included 10,206 women aged 18-39 who had either cervical intraepithelial neoplasia grades 2-3 or adenocarcinoma in situ. Over time, the incidence of HPV 16/18 declined from 52.7% in 2008—remembering that the vaccine was only introduced in 2006—to 44.1% in 2014.

These results demonstrate how, when the vaccine is used in the community, it has led—only a few years later—to a major reduction in two types of HPV which are highly related to the development of cervical cancer.

Cervical cancer takes many years to develop, so it will be years before we see an actual reduction in the incidence of cervical cancer

worldwide. However, with the substantial reduction we are seeing already in HPV 16/18, it is very clear that the vaccine is doing exactly what the clinical trials suggested.

One can only strongly encourage young adolescents—both young men and young women—to receive this incredibly effective and incredibly safe cancer prevention strategy.

I encourage all of you who are interested in the epidemiology of HPV and the stunning results of a major public health advance to review this paper in *Cancer Epidemiology, Biomarkers & Prevention*.

Thank you very much for your attention.

References

1. McClung NM, Gargano JW, Bennett NM, et al. Trends in human papillomavirus vaccine types 16 and 18 in cervical precancers, 2008-2014. Cancer Epidemiol Biomarkers Prev. 2019;28:602-609. Source

https://wb.md/2CYRqV4

Safe and Cheap Metformin Prevents Type 2 Diabetes Over 15 Years

Metformin continues to reduce the likelihood of developing type 2 diabetes among those at high risk for it over 15 years, particularly among those with higher baseline glycemia and women with a history of gestational diabetes mellitus (GDM).

Miriam E. Tucker

Findings from the long-term follow-up of participants in the landmark Diabetes Prevention Program (DPP) were recently published online in *Diabetes Care* by the DPP Research Group.

The diabetes prevention benefit of metformin was seen in both relative and absolute risk reduction and regardless of whether the diagnosis was made by oral glucose tolerance testing, fasting blood glucose, or HbA_{1c} (which was analyzed post-hoc as HbA_{1c} wasn't recommended for diagnosing diabetes when DPP started).

"Whichever method you use, you get this persistent and durable benefit with metformin. To me, that's the most important message," lead author David M. Nathan, MD, director of the Diabetes Center at Massachusetts General Hospital, Boston, told *Medscape Medical News* in an interview.

He added, "It's not just 3 or 10 years, as we reported before, but goes on for 15 years. That's a pretty powerful effect."

Cheap, Well-Tolerated With Powerful Effects, Especially in Subgroups

"Metformin remains this incredibly safe, inexpensive [agent], that's well-tolerated by most patients and it's really one of the few drugs in the world that makes sense for [diabetes] prevention, just because we know so much about it and have been using it for so long. That's why we selected it in the first place," Nathan explained.

Moreover, the current analysis identified two groups of high-risk patients who experienced even greater risk reduction with metformin: those with blood glucose measures on the higher glycemic end of the "prediabetes" ranges and women with a history of GDM. "That doesn't mean that others with prediabetes criteria don't benefit, but that some subgroups have even more benefit," Nathan noted.

However, he emphasized that use of metformin for diabetes prevention is off-label and because it's been off-patent for more than a decade it's unlikely that any pharmaceutical company would seek the indication. On the other hand, its low cost and safety record make it a desirable option as an adjunct to lifestyle approaches.

"There's certainly an overall resistance to taking medicine for disease prevention. But on the other hand, how is this different from taking statins or blood pressure medications to prevent heart disease?" he wonders.

"It really isn't different at all...This prevents diabetes, which is important because it leads to vision loss, renal failure, amputations, and heart disease. I think we would argue that preventing or

delaying or reducing the risk for diabetes is, in and of itself, important."

Diabetes Prevention Seen at 15 Years, Regardless of Analytic Method

In the original DPP trial, 3234 participants aged 25 years or older at high risk for type 2 diabetes were randomized to intensive lifestyle modification, metformin, or placebo. Of those, 1073 participants received metformin 850 mg twice daily and 1082 received masked placebo.

After DPP ended in 2001, all participants were offered a lower-intensity group version of the lifestyle intervention and those who had been randomized to metformin continued to take it during the observational follow-up, the Diabetes Prevention Program Outcomes Study (DPPOS).

All participants who develop diabetes during the DPPOS were referred back to their personal physicians, and many of those patients were again prescribed metformin.

Over the 15-year follow-up, the incidence of diabetes development was 17% lower among those in the original metformin group compared with the placebo group (hazard ratio, 0.83), with a rate difference of 21.25 cases/100 person-years, and diagnosis was based on a fasting and/or 2-hour glucose tolerance test.

When HbA_{1c} was used for diagnosis, metformin was associated with a 36% relative risk reduction (hazard ratio, 0.64) and an absolute rate difference of 21.67 cases/100 person-years (all statistically significant.)

The effect of metformin versus placebo didn't differ among those with baseline HbA_{1c} below 6% (hazard ratio, 0.61 vs 0.63).

But among those with HbA_{1c} 6.0% to 6.4%, metformin prevented significantly more cases of diabetes compared with those with an HbA_{1c} below 6% (rate difference, –3.88 vs –1.03 cases/100 person-years; P = .001).

And for women with a history of GDM, there was a significant 41% reduction in diabetes development with metformin versus placebo (hazard ratio, 0.59; P = .03). This relationship was even stronger by absolute rate difference (–4.57 vs –0.38/100 person-years, respectively; P = .01).

However, for parous women without a history of GDM the 6% difference between metformin and placebo wasn't significant (HR, 0.94).

No major differences in metformin's effect were seen by body mass index (BMI), and the benefit of metformin was lower in older age groups.

Will Metformin's Label Be Changed?

Nathan noted that another trial taking place in the United Kingdom, the Glucose Lowering in Non-diabetic Hyperglycaemia Trial (GLINT), is examining whether metformin prevents cardiovascular outcomes in people at high risk for type 2 diabetes. Results are expected in December 2024.

But even if that trial combined with other data show further benefit for using metformin in people at high risk for developing type 2 diabetes, there's no financial incentive for any pharmaceutical company to seek a label change by the US Food and Drug Administration or any other regulatory body worldwide.

However, there is another avenue in the United States: a "citizen's petition" to the FDA.

This was used by three academic institutions and, in April 2016, the agency loosened the chronic kidney disease (CKD) restrictions for metformin, allowing it to be used in patients with moderate CKD (30-60 mL/minute/1.73m^2).

"There is a movement underfoot to do the same for metformin as a preventative for diabetes," Nathan said. "The cost of medicines is in the headlines every day. Here's a drug that's generic and incredibly inexpensive that may be appropriate for repurposing...If more data

come out, it may be just what the drug companies hate — a drug that costs 10 cents a pill."

However, he also cautioned, "remember what happened with aspirin...wonder drugs still need careful consideration of the data."

During the DPP and DPPOS, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health provided funding to the clinical centers and coordinating center for the design and conduct of the study and collection, management, analysis, and interpretation of the data. Bristol-Myers Squibb and Parke-Davis provided additional funding and material support during the DPP. McKesson BioServices, Matthews Media Group, and the Henry M. Jackson Foundation for the Advancement of Military Medicine provided support services. Nathan has reported receiving study funding from Alere, now part of Abbott.

Diabetes Care. Published online March 15, 2019. Full text

http://bit.ly/2HYYUmu

Ancient 'Snowball Earth' thawed out in a flash

Geologically fast event that may have implications for today's human-driven global warming

By Lucas Joel Apr. 2, 2019 , 10:50 AM

More than half a billion years ago, our planet was a giant snowball hurtling through space. Glaciers blanketed the globe all the way to the equator in one of the mysterious "Snowball Earth" events geologists think occurred at least twice in Earth's ancient past. Now, scientists have found that the final snowball episode likely ended in a flash about 635 million years ago—a geologically fast event that may have implications for today's human-driven global warming.

***An artist's impression of what Earth looked like during the Snowball Earth glaciations.* Julio Lacerda/Studio 252MYA**

The ice, which built up over several thousand years, "melted in no more than 1 million years," says Shuhai Xiao, a paleobiologist at Virginia Polytechnic Institute and State University in Blacksburg who was part of the team that made the discovery. That's the blink of an eye in our planet's 4.56-billion-year history, suggesting the globe reached a sudden tipping point, Xiao says. Although the team doesn't know for certain what caused it, carbon dioxide emitted by ancient volcanoes may have triggered a greenhouse event, causing the ice sheets to thaw rapidly.

To shine light on the pace of deglaciation, Xiao and colleagues dated volcanic rocks from southern China's Yunnan province. These were embedded below another kind of rock called a cap carbonate—unique deposits of limestone and dolostone that formed during Snowball Earth's shutdown in response to high levels of carbon dioxide in the atmosphere. Using radiometric dating techniques, the team found the volcanic rocks were 634.6 million years old, give or take about 880,000 years. Alone, this single new date couldn't reveal the speed at which the melting happened. But in 2005, a different team of scientists dated volcanic rocks from *above* a similar cap at a different location—in China's Guizhou province. They were dated to 635.2 million years, give or take 570,000 years.

Together, the two samples suggest the melting event was a quick thaw of about 1 million years, Xiao and his colleagues wrote last month in *Geology*. The key, Xiao explains, is that these two dates are far more precise than those of past samples, with error bars of less than 1 million years. Those error bars essentially bracket the period in which the cap carbonates formed—and, thus, bound the period of the final Snowball Earth thawing event. Because previously discovered samples have error bars of several million years or more, Xiao says these new dates are the first that can be used to calculate the pace of melting with any certainty.

However, because the two new samples come from southern China, they don't paint a global picture of the ancient thaw, says Carol Dehler, a geologist at Utah State University in Logan. To do that, scientists would need to find datable volcanic rocks from other

parts of the world, which are about "as common as unicorns," she jokes. But, she adds, they might be out there "waiting to be discovered."

Meanwhile, understanding the nature of these ancient glaciations could help scientists dealing with climate change today: "I think one of the biggest messages that Snowball Earth can send humanity," Dehler says, "is that it shows the Earth's capabilities to change in extreme ways on short and longer time scales."

http://bit.ly/2UlW6qs

FDA slams homeopaths for uncontrolled snake venom, germs in kids' products

FDA warns companies to clean up amid ongoing crackdown.

Beth Mole - 4/3/2019, 1:53 AM

In an ongoing crackdown on dubious homeopathic products, the US Food and Drug Administration posted warning letters on Monday to four homeopathic companies the agency said committed violations that put consumers at risk, including lacking quality controls for products containing snake venom as well as skipping safety testing for products intended for children.

"We're committed to continue taking appropriate actions when we believe patients are being put at risk by products that contain potentially harmful ingredients or have significant quality issues," FDA Commissioner Scott Gottlieb said in a statement.

One of the chided companies, Red Mountain Incorporated, based in Florida, was found to lack all quality controls for its homeopathic product said to contain components of snake venom. "Without an adequate QU [Quality Unit], you lack the ability to ensure the safety, identity, strength, quality, and purity of your drug product," the agency wrote in its letter.

The product in question is called Bioven. Red Mountain claims without documented evidence that it can treat "Rheumatoid Arthritis, AIDS, Hepatitis B & C, Bursitis, some Cancers and Lupus" by "reversing the body's chemical and immunological imbalances."

Red Mountain did not respond to Ars' request for comment.

Bioven should, in the abstract, be harmless. The foundations of homeopathy are that certain substances (often toxic ones) can treat an illness if the substance causes similar symptoms to the illness ("like cures like")—but only in absurdly large dilutions. Homeopaths erroneously believe that "ultradilutions" plus "vigorous shaking" increase the potency of a substance and lead to an effective treatment. Many homeopathic products are diluted far beyond the point at which any starting material still remains. In other words, they're just water.

But if the products aren't properly diluted, any toxic starter substances can be dangerous. That appeared to be the case for improperly diluted homeopathic teething products that contained the toxic substance belladonna, aka deadly nightshade. After years of investigations, the FDA linked the products to the deaths of 10 babies, as well as illnesses in more than 400 others in 2016. The tragic cases, in part, raised concern over the industry and spurred the agency to step up its regulatory oversight in 2017. The FDA is particularly sensitive to homeopathic products aimed at children in wake of the scandal.

In the latest batch of warning letters, the agency warned Tec Laboratories Incorporated over safety issues it found with the company's homeopathic children's product "LiceFreee Spray!" The spray is said to kill head lice, including "SUPER LICE" and lice eggs. The active ingredient in the spray is Natrum muriaticum, which is homeopathic-speak for sodium chloride, aka table salt.

Though table salt isn't as concerning as other homeopathic ingredients, the FDA says that Tec Laboratories didn't do standard testing to make sure its lightly salted spritz didn't contain harmful microbial contaminants. The agency also said that the company

failed to follow up on test results that indicated “high microorganism levels” in their facility’s water system.

In a response emailed to Ars, Tec Labs said it is "working with the Food and Drug Administration to address issues raised" in the warning letter. The company added that it is committed to complying to FDA requirements and "ensuring the quality, safety, efficacy, and purity of their products."

Similarly, the FDA further rebuked King Bio for ongoing microbial contamination issues at its facility in North Carolina. Last year, the agency spurred the large homeopathic maker to recall more than 900 products over contamination concerns. Still, the FDA says that the company has failed to resolve the problems and continues to pose a risk to consumers.

The warning letter to King Bio notes:

You manufacture and distribute hundreds of drugs including those intended for infants, children, pregnant women, and immunocompromised individuals. Over multiple years, your firm obtained recurring test results for water used as a component of your drugs, as well as results for finished homeopathic drug products, outside of microbiological limits. This testing revealed extremely high levels of microbiological contamination, including results that were Too Numerous to Count (TNTC), and identified the presence of significant opportunistic pathogens in your drugs. Furthermore, your tests of retained samples and customer complaint bottles found objectionable microbiological contamination in already distributed lots.

At the time of the recalls, King Bio’s founder and president, naturopath Frank King, said that the company “chose to issue the recall out of an abundance of caution.”

Lastly, the FDA sent a warning letter to B. Jain Pharmaceuticals, which makes ear ring relief drops. The agency noted that its investigators observed “numerous flying insects” in the company’s facility and ingredients.

The post has been updated to include a response from Tec Labs.

http://bit.ly/2WMXDma

PSU study finds that money, revenge, morals motivate whistleblowers to expose tax fraud

Nearly 12,000 whistleblowers reported tax fraud to the IRS in 2017

Revenge-seeking ex-lovers, jilted business partners and vindictive former employees are among the nearly 12,000 whistleblowers who reported tax fraud to the IRS in 2017. An estimated $3 trillion dollars is lost worldwide in tax evasion every year.

A study by Portland State University School of Business accounting professor Cass Hausserman finds that people who expose others of tax fraud often do so as revenge that's disguised as their moral obligation. Blowing the whistle is also motivated by a financial gain for the whistleblower. Revenge is commonly considered a primary reason why whistleblowers report tax fraud--so much so, that it's often referred to as "the revenge tax."

Hausserman's study, "The influence of revenge and financial rewards on tax fraud reporting intentions," revealed that whistleblowers often justify or disguise their revenge through a re-framing of the motivation into a moral obligation. The study published in the March edition of the Journal of Economic Psychology.

"People with a revenge motive justify their decision as moral obligation when they plan to blow the whistle on a colleague for tax fraud. They most likely feel better about reporting someone because it's their 'moral duty' rather than for a more negative reason, such as revenge," said Hausserman.

What does this tell us? When revenge is disguised as moral obligation, it's sweeter than money.

Research on the impact that financial incentive can have on a revenge motivation is limited. Money, as a single factor, has been

extensively shown through research to increase the reporting of wrongdoing, according to a 2012 study by Bowles & Polania-Reyes. According to previous research, financial incentives may weaken intrinsic motivation. This effect is called "hijacking"-- when an individual shifts their decision-making based on an economic choice (cash reward) rather than a moral obligation.

Participants with a financial incentive motive were 28 percent more likely to blow the whistle than those without a revenge or financial motivation. Participants with a revenge motive were roughly 25 percent more likely to blow the whistle than those without financial or revenge motivation.

Moral obligation alone (without revenge) was the most important factor in tax fraud reporting and increased whistleblowing 1.5 to 2 times more than just a financial incentive. Moral obligation and financial incentives both independently and together encourage whistleblowing. Adding a revenge motive encouraged it even more.

In an effort to recoup some of the loss through tax evasion, many companies have created numerous whistleblowing programs where individuals can confidently report either known or suspected fraud.

Hausserman suggests that research can expand on this phenomenon into other disciplines, such as whistleblowing related to discrimination or sexual harassment, where there is likely a negative motivating emotion.

The study's co-authors include Jonathan Farrar from Ryerson University and Morina Rennie from University of Regina.

http://bit.ly/2K5ulqM

Blocking protein's activity restores cognition in old mice, Stanford study shows

By blocking a protein's activity with antibodies, Stanford University School of Medicine investigators were able to improve cognitive behavior in aging mice.

A paper describing the finding will be published online April 3 in *Nature*. Tony Wyss-Coray, PhD, professor of neurology and neurological sciences, is the senior author. The lead author is MD-PhD student John Pluvinage.

Wyss-Coray has been working for several years on the question of what causes the brain to lose its acuity with advancing age. One focus of his research has been a class of brain cells called microglia, which serve both as the brain's immune cells and its garbage crew. Among the many different things microglia do to keep the brain healthy is scarfing up bits of cellular debris and protein deposits that build up in the course of normal metabolic activity.

On average, the garbage-collecting performance of microglia diminishes in aging brains. Why this happens, and the extent to which the faulty garbage service is actually responsible for age-related cognitive losses, are unclear. But it's a decent bet that one way or another, microglial malperformance plays a role in neurodegeneration, said Wyss-Coray, the D. H. Chen Professor II and a senior research career scientist at the Veterans Affairs Palo Alto Health Care System.

"Many of the genes whose high-risk variants have recently been linked to Alzheimer's disease are known to be active in the brain only in microglia," he said. "Microglial genes' activation patterns are abnormal in Alzheimer's patients, and in other neurodegenerative disorders including Parkinson's disease and amyotrophic lateral sclerosis. "We think we may have discovered a way to get these cells back on track and make them work the way they used to when we were young."

The ingest-then-digest procedure employed by microglia and other immune-cell types in the body is called phagocytosis. The study used laboratory techniques to identify mouse genes whose activity either impairs or enhances microglial phagocytosis and whose activity levels either increase or decrease substantially with age.

Blocking genes' functionality

The investigators picked about 3,000 genes encoding proteins that they judged could be targeted by drugs or that had already been the focus of drug development. One at a time, they blocked each gene's ability to encode a protein. The goal was to learn how each blockade affected the ability of cultured microglia from mice to ingest small particles of fluorescently labeled latex. (The brighter a microglial cell glowed, the better a refuse eater it was.)

"It was like examining the books of the garbage-hauling company," Wyss-Coray said. "We wanted to know: 'Is it the garbage truck's faulty wheels? The rusty containers? An unanticipated garbage overflow? Lazy or poorly trained staff? Or is the street in bad shape?'"

In a parallel experiment, the investigators determined which of those approximately 3,000 genes are more or less active in microglia from the hippocampi of young mice versus old mice. (The hippocampus is a brain structure, one on each side of the brain, that's essential to learning and memory.)

Surprisingly, when the scientists compared the results of both experiments, they found just one gene that affected microglial phagocytosis and whose activity in microglia substantially increased with advancing age. Older microglia produced far more copies of this gene -- a proxy for upregulated production of the protein for which the gene is a blueprint -- than younger ones did, and knocking out its function greatly improved microglial phagocytosis.

"Now we had a tentative suspect, a gene that had never before been implicated in microglial garbage removal," Wyss-Coray said. So they zeroed in on this gene, called CD22, which is found in both mice and humans.

In a follow-on experiment, the CD22 protein turned up three times as often on the surface of older mice's microglia as on those of younger mice's microglia, confirming the gene-activity finding. These proteins could be blocked by antibodies, molecules that bind to a specific protein and can be generated in the lab. Antibodies are bulky and don't easily penetrate cells, but they're excellent for targeting cell-surface proteins.

Injecting antibodies

Wyss-Coray's team injected antibodies to the CD22 protein into the hippocampus on one side of mice's brains. They also injected similar antibodies that were incapable of binding to CD22 into the hippocampus on the opposite side.

Along with the antibodies, the scientists administered fluorescence-labeled bits of myelin. This substance coats numerous nerve cells, for which it provides insulation. But myelin debris accumulates in aging brains and has been shown to overwhelm microglia's ability to clear it away.

Wyss-Coray and his associates found that, 48 hours later, the myelin bits they'd injected into the mice's hippocampi were far less prevalent on the side where they had administered CD22-blocking antibodies rather than "dummy" antibodies.

"Microglia are the only cells in mice's brain that actually express the CD22 protein, so this difference is likely due to the CD22-blocking antibodies' effect on microglia," Pluvinage said.

The investigators conducted analogous experiments, substituting a protein called beta-amyloid, whose buildup in the brain is a hallmark of Alzheimer's disease, and alpha-synuclein, another protein similarly associated with Parkinson's disease. In both cases, microglia exposed to CD22-blocking antibodies outperformed their peers on the opposite side of the brain in ingesting the neurodegeneration-linked substances.

Then, the researchers lengthened the period of exposure from 48 hours to a full month. They reconfigured their injection technique to provide continuous CD22-blocking antibody infusion on both

sides of the brain over this period. Along with a host of findings consistent with their earlier ones, Wyss-Coray's team observed that old mice receiving these infusions outperformed control mice of the same age on two different tests of learning and memory that are commonly used to assess mice's cognitive ability.

"The mice became smarter," Wyss-Coray said. "Blocking CD22 on their microglia restored their cognitive function to the level of younger mice. CD22 is a new target we think can be exploited for treatment of neurodegenerative diseases."

Stanford's Office of Technology Licensing has filed for a patent on intellectual property associated with the study.

Wyss-Coray is a member of the Wu Tsai Neurosciences Institute at Stanford, the Stanford Maternal & Child Health Research Institute and Stanford Bio-X and a faculty fellow of Stanford ChEM-H.

Other Stanford co-authors are postdoctoral scholars Michael Haney, PhD, Tal Iram, PhD, and David Gate, PhD; MD-PhD students Benjamin Smith and Liana Bonanno; undergraduate student Jerry Sun; medical student Madeleine Scott; graduate students David Morgens, Andrew Yang and Steven Shuken; research assistant Lulin Li; research associate Davis Lee; senior research scientist Jian Luo, MD, PhD; associate professor of bioinformatics and of biomedical data science Purvesh Khatri, PhD; professor of chemistry and ChEM-H director Carolyn Bertozzi, PhD; and assistant professor of genetics Michael Bassik, PhD.

The work was funded by the U.S. Department of Veterans Affairs, the National Institutes of Health (grants R01AG045034, DPAG053015, F30AG060 and S10OD020141), the NOMIS Foundation, the Glenn Foundation for Aging Research, the Cure Alzheimer's Fund, the Stanford University Medical Scientist Training Program and the Wu Tsai Neurosciences Institute.

Stanford's Department of Neurology and Neurological Sciences also supported the work.

http://bit.ly/2G23Hl1

Dementia type correlates with criminal behaviour

Study finds one type of neurodegenerative condition is significantly associated with law-breaking and inappropriate acts.

Andrew Masterson reports.

People with frontotemporal dementia have a significantly elevated risk of committing criminal or socially inappropriate behaviour, Swedish research shows.

Furthermore, the appearance of criminal behaviour in a previously law-abiding person, the researchers suggest, might serve as a diagnostic warning signal that dementia is developing.

Frontotemporal dementia (FTD) is challenging to identify because it manifests in a range of symptoms that are similar to those of Alzheimer's Diseases (AD), and even unrelated conditions, such as stroke or depression. As with many neurodegenerative disorders, conclusive diagnosis can only be made during autopsy.

This was the approach used by researchers led by Madeleine Liljegren from Sweden's Lund University.

She and colleagues examined the pathologies of 220 people who had been diagnosed, post mortem, with either FTD or AD, and compared the results to their criminal and behavioural histories. The cohort comprised 119 cases of FTD, and 101 cases of AD.

Of the group, 58% were female, the median age of disease onset was 63, average age at death was 72, and the median length of time spent with either disease was nine years (although this ranged from one year to 28).

Instances of criminal behaviour were found in 65 of the 220 – the majority of them, 50, among the FTD sufferers. Also, some 89% of the criminally active FTD subset had committed more than one criminal act. The repeat rate in the AD criminals was significantly lower, at 53%.

The difference in instances of socially inappropriate behaviour was also significant. It was recorded on the records of 89 members of the FTD group, and 57 members of the AD group.

"These results suggest that criminal and socially inappropriate behaviours may be more prevalent and criminal behaviours may be more recurrent in patients with FTD than in those with AD," the authors conclude in a paper published in the *JAMA Network Open*.

"These findings may help with the clinical diagnostic process."

http://bit.ly/2IaElCZ

Alcohol-induced brain damage continues after alcohol is stopped

These results refute the current belief that changes in the brain begin to normalize immediately after stopping alcohol consumption

Although the harmful effects of alcohol on the brain are widely known, the structural changes observed are very heterogeneous. In addition, diagnostic markers are lacking to characterize brain damage induced by alcohol, especially at the beginning of abstinence, a critical period due to the high rate of relapse that it presents.

Now, a joint work of the Institute of Neuroscience CSIC-UMH, in Alicante, and the Central Institute of Mental Health of Mannheim, in Germany, has detected, by means of magnetic resonance, how the damage in the brain continues during the first weeks of abstinence, although the consumption of alcohol ceases.

The research, published today in JAMA Psychiatry, whose first author is Silvia de Santis, shows that six weeks after stopping drinking there are still changes in the white matter of the brain, as revealed by the neuroimaging study carried out on ninety voluntary patients interned for his rehabilitation treatment in a German hospital.

The results of this work are surprising, explains Dr. Santiago Canals, of the Institute of Neurosciences CSIC-UMH, who has coordinated the research: "Until now, nobody could believe that in the absence of alcohol the damage in the brain would progress".

Ninety patients with an average age of 46 years hospitalized because of an alcohol use disorder participated in this study. To compare the brain magnetic resonances of these patients, a control group without alcohol problems was used, consisting of 36 men with an average age of 41 years.

"An important aspect of the work is that the group of patients participating in our research are hospitalized in a detoxification program, and their consumption of addictive substances is controlled, which guarantees that they are not drinking any alcohol. Therefore, the abstinence phase can be followed closely", highlights Dr. Canals.

Another differential characteristic of this study is that it has been carried out in parallel in a model with Marchigian Sardinian rats with preference for alcohol, which allows to monitor the transition from normal to alcohol dependence in the brain, a process that is not possible to see in humans", explains Dr. De Santis.

The damages observed during the period of abstinence affect mainly the right hemisphere and the frontal area of the brain and reject the conventional idea that the microstructural alterations begin to revert to normal values immediately after abandoning the consumption of alcohol.

With the consumption of alcohol "there is a generalized change in the white matter, that is, in the set of fibers that communicate different parts of the brain. The alterations are more intense in the corpus callosum and the fimbria. The corpus callosum is related to the communication between both hemispheres. The fimbria contains the nerve fibers that communicate the hippocampus, a fundamental structure for the formation of memories, the nucleus accumbens and the prefrontal cortex, "explains Dr. Canals. The nucleus accumbens is part of the reward system of the brain and the prefrontal cortex is fundamental in decision making.

The researchers from Alicante and Germany now try to characterize the inflammatory and degenerative processes independently and more precisely, in order to investigate the progression during the early abstinence phase in people with alcohol abuse problems.

http://bit.ly/2uNwOCo

There May Be a Link Between Coffee and Lung Cancer, Study Suggests

New study suggests that there may be a downside to your morning brew

By Yasemin Saplakoglu, Staff Writer

ATLANTA — Drinking coffee has been linked to a slew of health benefits, such as a longer life span, and a decreased risk of conditions including depression, heart attacks and certain cancers.

But a new study suggests that there may be a downside to your morning brew: Researchers found that drinking two or more cups of coffee or tea may increase a person's risk of lung cancer.

The findings were presented on March 31, here at the annual meeting of the American Association for Cancer Research.

Of note, the link was even true for nonsmokers. Because people who smoke cigarettes are also more likely to drink coffee and tea, it was difficult in previous studies to disentangle the effects of these drinks from those of smoking, in developing lung cancer, said lead study author Jingjing Zhu, a Ph.D. student at Vanderbilt University in Tennessee.

In the new study, an international group of researchers analyzed data from 17 different studies that included a total of 1.2 million participants in the U.S. and Asia. The studies noted whether participants drank coffee or tea or smoked cigarettes. About half were nonsmokers.

The participants were tracked for an average of 8.6 years. During that time, more than 20,500 participants developed lung cancer.

The researchers found that nonsmokers who drank two or more cups of coffee a day had a 41 percent higher risk of lung cancer than those who didn't drink coffee. Similarly, nonsmokers who drank two or more cups of tea a day had a 37 percent greater risk of lung cancer than non-tea drinkers. (Because data was taken from multiple studies, the exact definition of a cup varied.)

The study also found that a person's risk didn't change significantly between ages, races or the type of coffee people drank — both decaf and caffeinated coffee seemed to be associated with similar risks. In fact, decaf coffee was associated with a 15 percent higher risk than caffeinated coffee, Zhu said.

Still, Zhu noted that "this [was] only an observational study" and didn't prove cause-and-effect. But the researchers hypothesize that it isn't caffeine that's behind the link. Instead, it may be that something in the roasting process is driving the link between coffee and lung cancer risk, Zhu told Live Science.

The study had several limitations. For example, although the participants were tracked for years after the studies started, data on smoking and coffee and tea intake was measured only one time, at the beginning of the studies. So if people changed their behaviors throughout the years, it could have skewed the results, Zhu said.

What's more, if nonsmokers were exposed to second-hand smoke — which wasn't accounted for but could also increase lung cancer risk — that could have also skewed the results, she said.

Dr. Julie Fisher, an oncologist at the Levine Cancer Institute in North Carolina who was not part of the study, said that the findings were "interesting" and "compelling," but noted that because it's an association finding, she "certainly would not draw conclusions based on this."

However, though there's still much more research needed, Fisher told Live Science that she agreed that "maybe there's something in the [coffee brewing] process" that's driving the link.

Other coffee findings presented at the meeting were more comforting: Drinking coffee wasn't associated with an increased risk of glioma or colorectal cancer in men and women; nor was it associated with bladder cancer or renal cell carcinoma in male

smokers. Coffee was found to be associated with a lower risk of breast cancer in post-menopausal women and tea with a lower risk of glioma in women. In both men and women, decaf coffee was found to be associated with a lower risk of colorectal cancer.

The findings have not yet been published in a peer-reviewed journal.

https://bbc.in/2uNhupe

Bowel cancer: Self-testing kit 'saved my life'

A mother-of-three says a self-testing kit for bowel cancer saved her life.

Wendy Lyons, lives in Eastwood, Nottinghamshire, a county leading the way in the use of Faecal Immunochemical Tests or FIT.

The kit can tell doctors whether a more expensive and uncomfortable colonoscopy is needed.

Hospital bosses hope they can use it to find cancer earlier in people who would not normally be tested for the disease.

Clinical commissioning groups (CCGs) in Nottinghamshire said in November 2017, Nottingham GPs were the first in England to offer tests to patients with symptoms of bowel cancer other than spots of blood in their faeces or an obvious lump.

The test, which costs the NHS about £15 per person compared with £400 for a colonoscopy, is this year being sent to everyone over 60 as part of the national screening programme and is already widely used in Scotland.

But in Nottinghamshire, doctors can recommend the test to anyone with unexplained bowel problems, even if they think there is only a slim chance they have cancer, meaning they can pick it up in younger people too.

'Luckiest survivor alive'

Miss Lyons, 46, thought she was going through the menopause when she started getting headaches and pains. Her GP initially reassured her it was unlikely to be cancer, offering her the test as a precaution. It showed up positive and as a result her cancer was picked up so early she avoided both chemotherapy and major side effects from her operation.

"I feel like the luckiest cancer survivor alive - I can't thank the NHS enough," she said. "That FIT test saved my life."

According to Ayan Banerjea, a bowel cancer consultant in Nottingham, GPs can be reluctant to recommend colonoscopies unless it is necessary. Using the kit, you collect small samples of your faeces and post them to a lab which then checks them for tiny amounts of blood, which could be caused by cancer.

A small number of places now follow Nottingham's example, such as hospitals in Hertfordshire and Leicester, but most are waiting to see how well it works first, according to Mr Banerjea.

Bowel cancer is the fourth most common cancer in the UK and came under the spotlight after BBC journalist Jeremy Bowen's diagnosis. Mr Banerjea said medics were now "picking up more cancers at an earlier stage".

http://bit.ly/2uQTmlA

Experimental therapy completely clears HPV in one-third of cervical cancer precursors

Clinical trial shows promise of immune treatment against HPV infections that lead to cancer

ANN ARBOR, Michigan -- A potential new immune-based therapy to treat precancers in the cervix completely eliminated both the lesion and the underlying HPV infection in a third of women enrolled in a clinical trial.

The shot, a therapeutic vaccine, injects a specific protein that triggers an immune system response to attack high-risk HPV types that cause nearly all cervical cancer precursors, known as cervical intraepithelial neoplasia, or CIN.

"There are very few products trying to cure women who already have an HPV infection," says Diane Harper, M.D., M.P.H., M.S., professor of family medicine and obstetrics and gynecology at

Michigan Medicine. "It's very exciting. This is the first time we've seen something with this success rate that is relatively easy to implement."

Cervical precancerous lesions are divided into three grades of severity: CIN 1 lesions generally clear up on their own. CIN 2 lesions often clear up on their own, but can also progress to CIN 3 lesions. CIN 3 is the most severe. It's a very slow-growing disease, though: fewer than half of CIN 3 lesions will have become cancer within 30 years.

"But we have no way to determine which women with CIN 3 will progress to cancer and which women will not. So we treat all women with CIN 2 or 3 as if they are likely to develop cancer," Harper says.

The study enrolled 192 women diagnosed with CIN2 or CIN3, randomizing 129 to receive the vaccine and 63 to receive a placebo. Women were given three shots in their thigh, one per week for three weeks. Six months later, the women were treated with standard surgical procedures for CIN 2/3 and the removed tissue was examined.

Women who received the vaccine were more than twice as likely as those who received placebo to see their CIN eliminated regardless of the type of HPV infection. The results were most striking in the more-severe CIN3: at least 15 percent and as much as 36 percent of those who got the vaccine saw their CIN3 eliminated, while none of the women in the placebo group did.

Researchers followed the participants for another two and a half years after surgery, the longest any study has followed women in these trials. They showed that long-term follow-up was better for those who received vaccine over placebo, with more women in the vaccine group remaining completely clear of HPV. The study is published in Gynecologic Oncology.

Harper notes that the therapeutic vaccine, called Tipapkinogen Sovacivec, or TS, is completely different from Gardasil9, the vaccine given to prevent HPV infection. While Gardasil9 prevents HPV infection from occurring, TS clears tissue already infected with HPV. CIN2 and CIN3 are always caused by high-risk HPV infections.

The typical treatment procedure for CIN2 or CIN3 involves removing a cone-shaped piece of the cervix, called a LEEP or a cone. This results in scarring and a shortened cervix, which can cause problems during childbirth and lead to increased risk of caesarean section. In addition, women who have this procedure have a very high risk of developing cervical cancer over the next 20 years if they do not continue to be screened.

"The surgical procedure removes all the tissue that is headed towards cancer, but it doesn't remove all the HPV. You're not home-free. You still have HPV," says Harper, an internationally recognized HPV researcher and member of the University of Michigan Rogel Cancer Center and senior associate director of the Michigan Institute of Clinical and Health Research (MICHR).

With the vaccine, researchers found that it not only eliminated the lesions but also eliminated the HPV infection.

"It actually treats the cause of the disease, which is HPV," Harper says.

Women who received the vaccine injections reported sometimes-severe reactions at the injection site. Harper says that was expected, because the vaccine is designed to trigger the immune system. An immune reaction is likely to inflame the skin.

The study looked only at cervical lesions, but HPV is linked to several other types of cancer, including head and neck cancer and anal cancer. The researchers envision testing TS for these cancers in the future. Additional clinical trials are needed before seeking

approval for TS from the U.S Food and Drug Administration. No trials are currently available.

Additional authors: Pekka Nieminen, Gilbert Donders, Mark H. Einstein, Francisco Garcia, Warner K. Huh, Mark H. Stoler, Katerina Glavini, Gemma Attley, Jean-Marc Limacher, Berangere Bastien, Elizabeth Calleja

Funding: F Hoffmann-La Roche LTD

Disclosure: The study was funded by Roche, who sold the compound to Transgene. Transgene facilitated the data analysis with Harper

Reference: Gynecologic Oncology, doi: 10.1016/j.ygyno.2019.03.250; published online April 4, 2019

http://bit.ly/2UiImMW

Does your cat know its name? Here's how to find out

As soon as they hear their name, most move their ears and heads

By David Grimm Apr. 4, 2019 , 9:00 AM

Give this a shot at home: Say four random words to your cat—separated by about 15 seconds—with the same length and intonation as its name. Then say its actual name. If it swivels its ears or perks up its head, chances are it knows what you call it.

That's essentially what researchers did in a new study. Japanese scientists played recordings of a cat's owner saying four words with lengths and accents similar to its name before saying the feline's actual name. The word *hihu* (Japanese for "skin"), for example, might precede the name "Kari." As the random words—all nouns—played, the cats became less and less interested. But as soon as they heard their name, most moved their ears and heads; a few even got up (above). The scientists saw similar responses when the cat's name came after the names of other felines he lived with, or when a stranger spoke the words.

Cats may recognize their names because it's the word humans say most frequently to them, or because it's often associated with something positive, like petting or food, the researchers say. Indeed, the only cats that had trouble with the task were those that lived in a cat café, a shop that can house dozens of cats that customers pay to hang out with. These felines could distinguish their name from random nouns, but not from the names of the cats they shared the café with. Perhaps that's because visitors call the names of many cats, but only "reward" a few with pets or treats, the scientists speculate.

The findings are the first to experimentally show that cats have some understanding of what we are saying to them, the team concludes today in *Scientific Reports*. Trained cats may understand words like "sit" or "jump," but it could be because humans are using additional cues, such as hand gestures. The new findings could improve our relationships with our pets, the researchers say; cooing your cat's name during a stressful vet visit, for example, might help reassure it. Still, whether cats understand that their name is really *their name* remains unclear. They may just think it's another word for "treat."

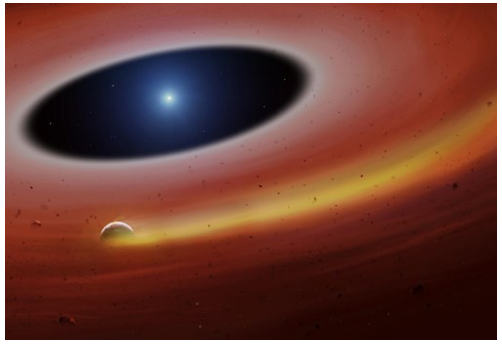
http://bit.ly/2U5RqA0

Heavy metal planet fragment survives destruction from dead star

A fragment of a planet that has survived the death of its star has been discovered by University of Warwick astronomers in a disc of debris formed from destroyed planets, which the star ultimately consumes

- ***Planetary fragment identified in a disc of debris circling a dead star 400 light years away***
- ***Thought to be rich in heavy metals iron and nickel which helped it survive destruction of its planetary system***
- ***Astronomers from University of Warwick detected the small body orbiting a white dwarf 'closer than we would expect to find anything still alive'***
- ***Planetesimal orbits with a 'comet-like tail' of gas, creating a ring within the debris disc***

- ***Offers a hint as to the future of our Solar System, 6 billion years from now***



A fragment of a planet that has survived the death of its star has been discovered by University of Warwick astronomers in a disc of debris formed from destroyed planets, which the star ultimately consumes.

A planetary fragment orbits the star SDSS J122859.93+104032.9, leaving a tail of gas in its wake. **University of Warwick/Mark Garlick**

The iron and nickel rich planetesimal survived a system-wide cataclysm that followed the death of its host star, SDSS J122859.93+104032.9. Believed to have once been part of a larger planet, its survival is all the more astonishing as it orbits closer to its star than previously thought possible, going around it once every two hours.

The discovery, reported in the journal *Science*, is the first time that scientists have used spectroscopy to discover a solid body in orbit around a white dwarf, using subtle variations in the emitted light to identify additional gas that the planetesimal is generating.

Using the Gran Telescopio Canarias in La Palma, the scientists studied a debris disc orbiting a white dwarf 410 light years away, formed by the disruption of rocky bodies composed of elements such as iron, magnesium, silicon, and oxygen - the four key building blocks of the Earth and most rocky bodies. Within that disc they discovered a ring of gas streaming from a solid body, like a comet's tail. This gas could either be generated by the body itself or by evaporating dust as it collides with small debris within the disc.

The astronomers estimate that this body has to be at least a kilometre in size, but could be as large as a few hundred kilometres in diameter, comparable to the largest asteroids known in our Solar System.

White dwarfs are the remains of stars like our sun that have burnt all their fuel and shed their outer layers, leaving behind a dense core which slowly cools over time. This particular star has shrunk so dramatically that the planetesimal orbits within its sun's original radius. Evidence suggests that it was once part of a larger body further out in its solar system and is likely to have been a planet torn apart as the star began its cooling process.

Lead author Dr Christopher Manser, a Research Fellow in the Department of Physics, said: "The star would have originally been about two solar masses, but now the white dwarf is only 70% of the mass of our Sun. It is also very small - roughly the size of the Earth - and this makes the star, and in general all white dwarfs, extremely dense.

"The white dwarf's gravity is so strong - about 100,000 times that of the Earth's - that a typical asteroid will be ripped apart by gravitational forces if it passes too close to the white dwarf."

Professor Boris Gaensicke, co-author from the Department of Physics, adds: "The planetesimal we have discovered is deep into the gravitational well of the white dwarf, much closer to it than we would expect to find anything still alive. That is only possible because it must be very dense and/or very likely to have internal strength that holds it together, so we propose that it is composed largely of iron and nickel.

"If it was pure iron it could survive where it lives now, but equally it could be a body that is rich in iron but with internal strength to hold it together, which is consistent with the planetesimal being a fairly massive fragment of a planet core. If correct, the original body was at least hundreds of kilometres in diameter because it is only at that point planets begin to differentiate - like oil on water - and have heavier elements sink to form a metallic core."

The discovery offers a hint as to what planets may reside in other solar systems, and a glimpse into the future of our own.

Dr Christopher Manser said: "As stars age they grow into red giants, which 'clean out' much of the inner part of their planetary system. In our Solar System, the Sun will expand up to where the Earth currently orbits, and will wipe out Earth, Mercury, and Venus. Mars and beyond will survive and will move further out.

"The general consensus is that 5-6 billion years from now, our Solar System will be a white dwarf in place of the Sun, orbited by Mars, Jupiter, Saturn, the outer planets, as well as asteroids and comets. Gravitational interactions are likely to happen in such remnants of planetary systems, meaning the bigger planets can easily nudge the smaller bodies onto an orbit that takes them close to the white dwarf, where they get shredded by its enormous gravity.

"Learning about the masses of asteroids, or planetary fragments that can reach a white dwarf can tell us something about the planets that we know must be further out in this system, but we currently have no way to detect.

"Our discovery is only the second solid planetesimal found in a tight orbit around a white dwarf, with the previous one found because debris passing in front of the star blocked some of its light - that is the "transit method" widely used to discover exoplanets around Sun-like stars. To find such transits, the geometry under which we view them has to be very finely tuned, which means that each system observed for several hours mostly leads to nothing. The spectroscopic method we developed in this research can detect close-in planetesimals without the need for a specific alignment. We already know of several other systems with debris discs very similar to SDSS J122859.93+104032.9, which we will study next. We are confident that we will discover additional planetesimals orbiting white dwarfs, which will then allow us to learn more about their general properties."

Dr Manser and Professor Gaensicke were supported by the European Research Council (ERC) under the EU's research and innovation programme (grant agreement 320964).

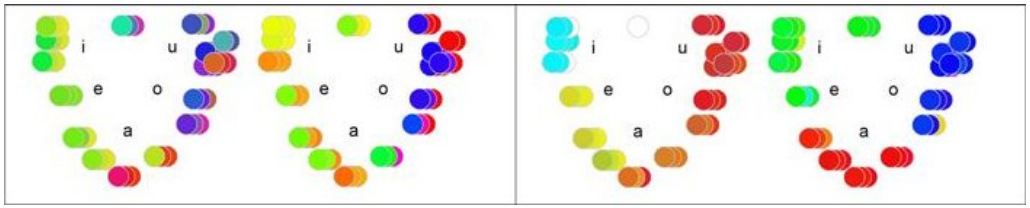
'A planetesimal orbiting within the debris disc around a white dwarf star' published in Science, *DOI: 10.1126/science.aat5330*

http://bit.ly/2WT3SEZ

Associating colors with vowels? Almost all of us do!

Does [a:] as in baa sound more green or more red? And is [i:] as in beet light or dark in colour?

Even though we perceive speech and colour are perceived with different sensory organs, nearly everyone has an idea about what colours and vowels fit with each other. And a large number of us have a particular system for doing so. This is shown in research by linguists from Radboud University and the University of Edinburgh on similarities in the vowel-colour associations perceived by over 1,000 people.



Vowel-color associations in two non-synesthete subjects (left) and in two synesthetes (right). Synesthetes more precisely chose the same color for a particular sound. However, all four participants created groups of sounds that lay close to a particular Dutch vowel, such as "ee" [i:] (upper left), and they all chose lighter colors for "ee" than for "aa" or "oo." General principles for vowel-color associations exist, whether one has synesthesia or not. **Mark Dingemanse Radboud University**

For the writer Vladimir Nabokov, "aa" was the colour of polished ebony and "ee" was yellow. Nabokov had synaesthesia: his sensory perceptions mingled with one another. In his case, he saw colours when hearing certain vowels, but many forms of synaesthesia are possible. Only 1 in 25 people have synaesthesia, but this new research shows that certain intuitions about "sound colours" shared by many more people than this.

"Aa" is more red than green

In this study, over 1,000 people took part in an online test where they chose colours for 16 spoken vowels. A large majority felt that "aa" was more red than green, and "ee" more light than dark, whether they had synaesthesia or not. According to Mark Dingemanse, one of the researchers, "There seems to be a logic to how we link sound and colour, and the structure of language has an important role in this process."

Vowel space

Sixteen vowels sounds like a lot, but it works like this. When you say "aa", then move to "oo" as in boot and then to "ee" as in beet, Dingemanse explains, you have visited the three outer points of what linguists call the vowel space. The 16 spoken sounds in our study were evenly distributed over this space.

Vowel system dictates colour associations

Earlier studies have found that colour associations are linked to the pitch of the sounds: the higher the pitch, the lighter the colour. But the new study shows that colour associations are driven to a greater degree by the vowel system of a language. For example, many participants described sounds that were close to the Dutch vowel "ee" as light green, while nearby sounds resembling "ay" as in say were assigned a different colour. The associations are shaped according to how our language carves up the vowel space.

Dingemanse says, "If colour associations were purely dependent on acoustical factors, the colours would neatly run into one another like in a rainbow. Instead, we see that sounds are grouped according to the way that our language carves up the vowel space: a few blue spots and then suddenly a red one, with no transition of blue-purple-red.

You could say that the vowels have to pass through the sorting machine that is our language before we can link colours to them, even in synaesthetes, for whom associations like these are involuntary."

Synaesthesia

The researchers used a new method to dig deeper into the structure of the colour associations. For each participant, they compared the chosen vowel-colour associations with a random sample of 10,000 random associations. They used this to measure how systematic the chosen associations were.

"Synaesthetes' associations were more systematic than those of non-synaesthetes," says Christine Cuskley of Edinburgh University. "But some patterns occur everywhere: people seem to align the vowel space and colour space with each other and connect the dots from one space to the other." For instance, colours chosen for "ee" and "ay" tend to be quite close to each other, while those for "aa" and "oo" are further apart. Automatic associations like those of synaesthetes therefore rely on some of the same principles that non-synaesthetes use to link vowels and colours.

The study took place as part of the so-called Great National Research Project (GNO), a collaborative venture of Radboud University, the Netherlands Organisation for Scientific Research (NWO) and NTR Broadcasting. In order to better understand the way in which our senses work together, it is necessary to examine a large number of subjects who represent all degrees of synaesthesia, from less to more.

This was made possible by the GNO, which was set up by Dingemanse and neurobiologist Tessa van Leeuwen of the Donders Institute in Nijmegen. With the support of the NWO, they developed software for performing quick online tests. The researchers made the software publicly available so that others could continue to work with it.

Future publications can thus share additional new insights into how synaesthesia works and how language influences our perception.

http://bit.ly/2OSrGpC

Researchers show that mutations in human livers can promote tissue regeneration

Genetic mutations accumulating in the adult liver can promote regeneration

***Watch video:** Researchers show that mutations in human livers can promote tissue regeneration*

DALLAS - Researchers at the Children's Medical Center Research Institute at UT Southwestern (CRI) have identified genetic mutations that accumulate in the adult liver that can promote regeneration in the context of chronic liver damage.

The widespread use of genome sequencing has led to the realization that normal tissues in healthy people accumulate spontaneous changes in DNA, known as somatic mutations, over time. This process has been well characterized in the blood-forming system, but it is unknown to what extent somatic mutations accumulate with age in most solid organs or what effect this buildup might have on organ regeneration.

"Mutations that arise in normal cells are most often viewed through the lens of cancer. While certain mutations can represent steps toward the development of cancer, other mutations may actually promote tissue healing without causing cancer," said Dr. Hao Zhu, an Associate Professor at CRI and of Internal Medicine and Pediatrics at UT Southwestern. Dr. Zhu, a corresponding author of the study published today in Cell, is also an attending physician in the Multidisciplinary Liver Cancer Clinic at Parkland Hospital.

The researchers used a variety of genetic techniques to identify mutated genes in patients with chronic liver disease and to evaluate whether the mutations affected liver cell function. Because the study of somatic mutations in normal tissues is still a relatively new field, Dr. Zhu and his collaborators needed to first develop some of the genetic techniques used to make these discoveries.

"Cancer sequencing has been performed for a long time, but normal tissue sequencing is still new to many researchers. Since there is no set method for identifying mutations in normal tissues, we had to develop our own," said co-corresponding author Dr. Tao Wang, an Assistant Professor of Population and Data Sciences and in the Center for the Genetics of Host Defense at UT Southwestern. Dr. Wang, a member of the University's Quantitative Biomedical Research Center, along with graduate student Tianshi Lu, developed computational methods to analyze the sequencing data generated in this study.

These approaches allowed researchers to find hundreds of mutations in liver samples obtained from patients at Parkland Hospital by co-authors Drs. Adam Yopp, Associate Professor of Surgery at UTSW, and Amit Singal, Associate Professor of Internal Medicine and Population and Data Sciences at UTSW. The researchers then used a new CRISPR genetic screening method on mouse livers to test the functional consequences of the mutations for liver regeneration. This search led to the identification of a handful of mutations that had pronounced effects on liver regeneration.

"The CRISPR screening method developed by Joyce Jia, a graduate student in my lab, was a critical piece of the study that allowed us to pinpoint important genes among a large number of candidates. Not only has this approach allowed us to examine the impact of somatic mutations found in people, we hope to use it to find new drugs to increase organ regeneration in humans," Dr. Zhu said.

Next, Dr. Min Zhu, one of the co-first authors of the study, deleted those top-ranked genes in the livers of mice to mimic the effects of mutations seen in human liver samples. Researchers found that these genetically altered livers were more regenerative after liver damage.

"We discovered that many mutations provided liver cells with fitness advantages, giving them an edge over nonmutated cells in terms of growth and survival after environmental insults," Dr. Hao Zhu said. "However, the most remarkable finding from our study was that some mutated genes with strong influences on regeneration are unlikely to promote cancer because they are rarely found to be mutated in liver cancer samples. This finding suggests that certain mutations are selected for in regenerating tissues during chronic injury that promote tissue fitness or regeneration without promoting the development of cancer."

This outcome is surprising, given that chronic tissue damage promotes the development of cancer, particularly in the liver, he added.

These results have implications for patients with chronic liver disease. Currently, these patients have limited treatment options and are at risk for developing liver cancer, one of the fastest growing causes of cancer death in the U.S. Understanding whether the frequency and types of mutations can predict cancer risk could someday allow doctors to identify patients with a higher risk for liver cancer and stimulate more efforts toward cancer detection or prevention. In addition, a better understanding of how mutated genes promote tissue growth and regeneration, without promoting cancer, could enable scientists to develop therapies to safely prevent the progression of liver disease.

Funding for this study was provided by the Cancer Prevention and Research Institute of Texas (CPRIT), Stand Up To Cancer, the Pollock Foundation, the National Institutes of Health, and other donors to the Children's Medical Center Foundation.

Co-authors from UT Southwestern Medical Center included Dr. Xin Luo, Data Scientist; Dr. Purva Gopal, Assistant Professor, Pathology; Lin Li, Senior Research Scientist, CRI; Mobolaji Odewole, Research Study Coordinator, Internal Medicine; Veronica Renteria, Research Study Coordinator, Internal Medicine; Dr. Sam Wang, Assistant Professor, Surgery; Mahsa Sorouri, Graduate Student; Dr. Justin Parekh, Assistant Professor, Surgery; and Dr. Malcolm MacConmara, Assistant Professor, Surgery. Dr. Singal holds the David Bruton, Jr. Professorship in Clinical Cancer Research and is a Dedman Family Scholar in Clinical Care.

Other contributors were Dr. Kai Ge and Dr. Younghoon Jang from the National Institute of Diabetes and Digestive and Kidney Diseases.

http://bit.ly/2D0ihHH

Researchers engineer a cost-effective treatment for neglected tropical disease

A fungus, an antibiotic, a parasite, and a cure

Researchers have turned a fungus into a disease-curing factory through modern genetic engineering and patience. The natural antibiotic is a promising cure for a neglected tropical disease called human African trypanosomiasis, or African sleeping sickness, that infects thousands of people in remote, rural areas of sub-Saharan Africa each year.

"Our collaboration started about four years ago, and we have finally achieved our goal," said Professor Ikuro Abe from the University of Tokyo Department of Pharmaceutical Sciences.

"The gene cluster in the fungus is unique -- through a simple genetic deletion, we have engineered a strain of the fungus that only produces high concentrations of the desired antibiotic," explained Abe.

Professor Kiyoshi Kita, who retired from the University of Tokyo in 2016, dedicated a large portion of his career to understanding and curing African sleeping sickness. Abe's research team joined the project due to their expertise in mapping the chemical paths that lead from genes to proteins inside cells.

Abe's research team used their biosynthesis pathway expertise to genetically modify the fungus so that it produces large quantities of one specific antibiotic.

The fungus *Acremonium egyptiacum* naturally produces two different types of antibiotic: one is toxic to humans, but the other was identified as a potential treatment for African sleeping sickness in 1996 in part by Kita, at the time working with collaborators at the Niigata College of Pharmacy.

Artificially synthesizing the antibiotic would not be cost effective and the more common method of using bacteria to produce the chemical is infeasible.

Abe's research team identified that the fungus's two antibiotics are both made from the same precursor molecule. After the precursor is created, two separate groups of enzymes produce the two different antibiotics.

Researchers can leave the precursor molecule and the genes responsible for the desired antibiotic completely unchanged by simply deleting the genes responsible for the other toxic antibiotic.

In every liter of fungus that researchers grow in the lab, the engineered strain of the fungus can produce 500 milligrams of antibiotic. "We think this is an exceptionally good production system," said Abe.

Researchers have applied for a patent on the engineered strain of fungus. Collaborators at the Kikkoman Corporation, best known for making soy sauce, will pursue industrial-scale growth of the genetically engineered fungus and purification of the antibiotic.

The desired antibiotic, ascofuranone, is also a candidate treatment for cancer.

About human African trypanosomiasis

People can develop African sleeping sickness by being bitten by a fly. The disease is caused by a parasite that moves from the flies, to patients' blood streams, and then into the nerves of patients' brains and spinal cords. The disease is often fatal within three years. The same parasite can also infect livestock animals.

The World Health Organization aims to eliminate human African trypanosomiasis as a public health problem by 2020.

https://www.who.int/trypanosomiasis_african/en/

Journal Article

Yasuko Araki, Takayoshi Awakawa, Motomichi Matsuzaki, Rihe Cho, Yudai Matsuda, Shotaro Hoshino, Yasutomo Shinohara, Masaichi Yamamoto, Yasutoshi Kido, Daniel K. Inaoka, Kisaburo Nagamune, Kotaro Ito, Ikuro Abe, and Kiyoshi Kita. 2019. Complete biosynthetic pathways of ascofuranone and ascochlorin in Acremonium egyptiacum. *PNAS Latest Articles. DOI: 10.1073/pnas.1819254116*
http://www.pnas.org/cgi/doi/10.1073/pnas.1819254116

Other research mentioned in this release

Nobuko Minagawa, Yoshisada Yabu, Kiyoshi Kita, Kazuo Nagai, Nobuo Ohta, Keiichi Meguro, Shigeru Sakajo, Akio Yoshimoto. 1996. "An antibiotic, ascofuranone, specifically inhibits respiration and in vitro growth of long slender bloodstream forms of Trypanosoma brucei brucei*": Molecular and Biochemical Parasitology 81: 127-136. DOI: 10.1016/S0166-6851(96)02797-1 https://doi.org/10.1016/S0166-6851(96)02797-1*

https://go.nature.com/2U1SLrp

The Inca bedecked their sacrificial guinea pigs with earrings

Finding confirms historic reports that the rodents were killed en masse at South American ceremonies.

Buildings at the Inca site of Tambo Viejo, on the south coast of what is now Peru, were constructed with a very special kind of sub-flooring — sacrificed guinea pigs.

The Inca empire was one of many around the world that carried out animal sacrifice to its gods.

This guinea pig was adorned by the Inca before its sacrifice roughly 400 years ago. **L. Valdez/Int. J. Osteoarchaeol.**

Excavations by Lidio Valdez at the Institute of Andean Studies in Berkeley, California, show that dozens of guinea pigs (*Cavia porcellus*) were ritually sacrificed there around 400 years ago.

The victims were adorned with necklaces and earrings made of orange, red, purple and brown strings. Some were wrapped in cotton rugs. The animals were covered with a layer of clean river sand — and might have been alive when buried. Clay floors were then built over the sand.

The site is so dry that the little mammals were neatly mummified, the colors of their string adornment still bright today. The findings help to confirm early Spanish accounts of the sacrifice of large numbers of guinea pigs by the Inca. *Int. J. Osteoarchaeol.* (2019)

http://bit.ly/2YUlQsu

Artificial intelligence can now emulate human behaviors – soon it will be dangerously good

When artificial intelligence systems start getting creative, they can create great things – and scary ones.

Ana Santos Rutschman*

Take, for instance, an AI program that let web users compose music along with a virtual Johann Sebastian Bach by entering notes into a program that generates Bach-like harmonies to match them.

Run by Google, the app drew great praise for being groundbreaking and fun to play with. It also attracted criticism, and raised concerns about AI's dangers.

My study of how emerging technologies affect people's lives has taught me that the problems go beyond the admittedly large concern about whether algorithms can really create music or art in general. Some complaints seemed small, but really weren't, like observations that Google's AI was breaking basic rules of music composition.

In fact, efforts to have computers mimic the behavior of actual people can be confusing and potentially harmful.

Impersonation technologies

Google's program analyzed the notes in 306 of Bach's musical works, finding relationships between the melody and the notes that provided the harmony. Because Bach followed strict rules of composition, the program was effectively learning those rules, so it could apply them when users provided their own notes.

The Google Doodle team explains the Bach program.

The Bach app itself is new, but the underlying technology is not. Algorithms trained to recognize patterns and make probabilistic decisions have existed for a long time. Some of these algorithms are so complex that people don't always understand how they make decisions or produce a particular outcome.

AI systems are not perfect – many of them rely on data that aren't representative of the whole population, or that are influenced by human biases. It's not entirely clear who might be legally responsible when an AI system makes an error or causes a problem.

Now, though, artificial intelligence technologies are getting advanced enough to be able to approximate individuals' writing or speaking style, and even facial expressions. This isn't always bad: A fairly simple AI gave Stephen Hawking the ability to communicate more efficiently with others by predicting the words he would use the most.

More complex programs that mimic human voices assist people with disabilities – but can also be used to deceive listeners. For example, the makers of Lyrebird, a voice-mimicking program, have released a simulated conversation between Barack Obama, Donald Trump and Hillary Clinton. It may sound real, but that exchange never happened.

From good to bad

In February 2019, nonprofit company OpenAI created a program that generates text that is virtually indistinguishable from text written by people. It can "write" a speech in the style of John F. Kennedy, J.R.R. Tolkien in "The Lord of the Rings" or a student writing a school assignment about the U.S. Civil War.

The text generated by OpenAI's software is so believable that the company has chosen not to release the program itself.

Similar technologies can simulate photos and videos. In early 2018, for instance, actor and filmmaker Jordan Peele created a video that appeared to show former U.S. President Barack Obama saying things Obama never actually said to warn the public about the dangers posed by these technologies.

Be careful what videos you believe.

In early 2019, a fake nude photo of U.S. Rep. Alexandria Ocasio-Cortez circulated online. Fabricated videos, often called

"deepfakes," are expected to be increasingly used in election campaigns.

Members of Congress have started to look into this issue ahead of the 2020 election. The U.S. Defense Department is teaching the public how to spot doctored videos and audio. News organizations like Reuters are beginning to train journalists to spot deepfakes.

But, in my view, an even bigger concern remains: Users might not be able to learn fast enough to distinguish fake content as AI technology becomes more sophisticated. For instance, as the public is beginning to become aware of deepfakes, AI is already being used for even more advanced deceptions. There are now programs that can generate fake faces and fake digital fingerprints, effectively creating the information needed to fabricate an entire person – at least in corporate or government records.

Machines keep learning

At the moment, there are enough potential errors in these technologies to give people a chance of detecting digital fabrications. Google's Bach composer made some mistakes an expert could detect. For example, when I tried it, the program allowed me to enter parallel fifths, a music interval that Bach studiously avoided. The app also broke musical rules of counterpoint by harmonizing melodies in the wrong key. Similarly, OpenAI's text-generating program occasionally wrote phrases like "fires happening under water" that made no sense in their contexts.

As developers work on their creations, these mistakes will become rarer. Effectively, AI technologies will evolve and learn. The improved performance has the potential to bring many social benefits – including better health care, as AI programs help democratize the practice of medicine.

Giving researchers and companies freedom to explore, in order to seek these positive achievements from AI systems, means opening up the risk of developing more advanced ways to create deception and other social problems. Severely limiting AI research could curb that progress. But giving beneficial technologies room to grow comes at no small cost – and the potential for misuse, whether to make inaccurate "Bach-like" music or to deceive millions, is likely to grow in ways people can't yet anticipate.

[**]*Assistant Professor of Law, Saint Louis University*

Disclosure statement

Ana Santos Rutschman does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond their academic appointment.

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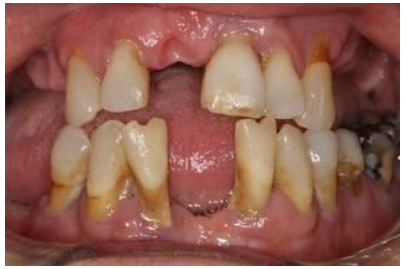
http://bit.ly/2KpUWWm

Gum bacteria implicated in Alzheimer's and other diseases

Scientists trace path of bacterial toxins from the mouth to the brain and other tissues

Orlando, Fla. - Researchers are reporting new findings on how bacteria involved in gum disease can travel throughout the body, exuding toxins connected with Alzheimer's disease, rheumatoid arthritis and aspiration pneumonia. They detected evidence of the bacteria in brain samples from people with Alzheimer's and used mice to show that the bacterium can find its way from the mouth to the brain.



The mouth of a person with severe gum disease. Bacteria involved in periodontitis have been linked with Alzheimer's disease, aspiration pneumonia, rheumatoid arthritis and other common disorders. **Image courtesy of Jan Potempa, University of Louisville.**

The bacterium, *Porphyromonas gingivalis*, is the bad actor involved in periodontitis, the most serious form of gum disease. These new findings underscore the importance of good dental hygiene as scientists seek ways to better control this common bacterial infection.

"Oral hygiene is very important throughout our life, not only for having a beautiful smile but also to decrease the risk of many serious diseases," said Jan Potempa, PhD, DSc, a professor at the University of Louisville School of Dentistry and head of the department of microbiology at Jagiellonian University in Krakow, Poland. "People with genetic risk factors that make them susceptible to rheumatoid arthritis or Alzheimer's disease should be extremely concerned with preventing gum disease."

While previous researchers have noted the presence of *P. gingivalis* in brain samples from Alzheimer's patients, Potempa's team, in collaboration with Cortexyme, Inc., offers the strongest evidence to date that the bacterium may actually contribute to the development of Alzheimer's disease. Potempa will present the research at the American Association of Anatomists annual meeting during the 2019 Experimental Biology meeting, held April 6-9 in Orlando, Fla.

The researchers compared brain samples from deceased people with and without Alzheimer's disease who were roughly the same age when they died. They found *P. gingivalis* was more common in samples from Alzheimer's patients, evidenced by the bacterium's DNA fingerprint and the presence of its key toxins, known as gingipains.

In studies using mice, they showed *P. gingivalis* can move from the mouth to the brain and that this migration can be blocked by chemicals that interact with gingipains. An experimental drug that blocks gingipains, known as COR388, is currently in phase 1 clinical trials for Alzheimer's disease. Cortexyme, Inc. and Potempa's team are working on other compounds that block enzymes important to *P. gingivalis* and other gum bacteria in hopes of interrupting their role in advancing Alzheimer's and other diseases.

The researchers also report evidence on the bacterium's role in the autoimmune disease rheumatoid arthritis, as well as aspiration pneumonia, a lung infection caused by inhaling food or saliva.

"*P. gingivalis*'s main toxins, the enzymes the bacterium need to exert its devilish tasks, are good targets for potential new medical interventions to counteract a variety of diseases," said Potempa. "The beauty of such approaches in comparison to antibiotics is that such interventions are aimed only at key pathogens, leaving alone good, commensal bacteria, which we need."

P. gingivalis commonly begins to infiltrate the gums during the teenage years. About one in five people under age 30 have low levels of the bacterium in their gums. While it is not harmful in most people, if it grows to large numbers the bacteria provoke the body's immune system to create inflammation, leading to redness, swelling, bleeding and the erosion of gum tissue.

Making matters worse, *P. gingivalis* even causes benign bacteria in the mouth to change their activities and further increase the immune response. Bacteria can travel from the mouth into the bloodstream through the simple act of chewing or brushing teeth.

The best way to prevent *P. gingivalis* from growing out of control is by brushing and flossing regularly and visiting a dental hygienist at least once a year, Potempa said. Smokers and older people are at increased risk for infection. Genetic factors are also thought to play a role, but they are not well understood.