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The Bonoi Academy of Science & Education (BASE)



THE BONOI ACADEMY OF SCIENCE & EDUCATION

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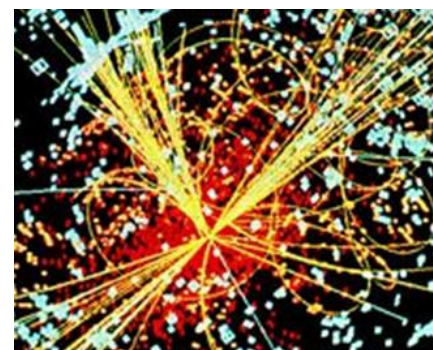
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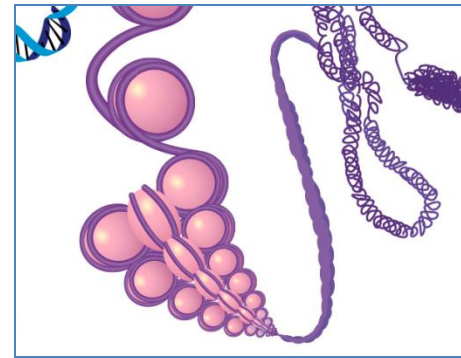
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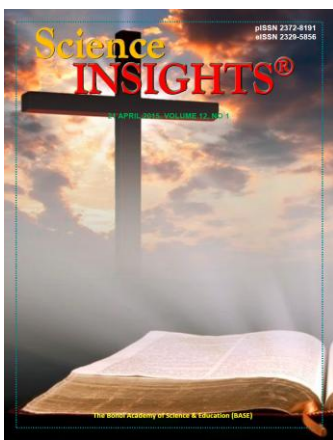
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Image: BASE illustrating group

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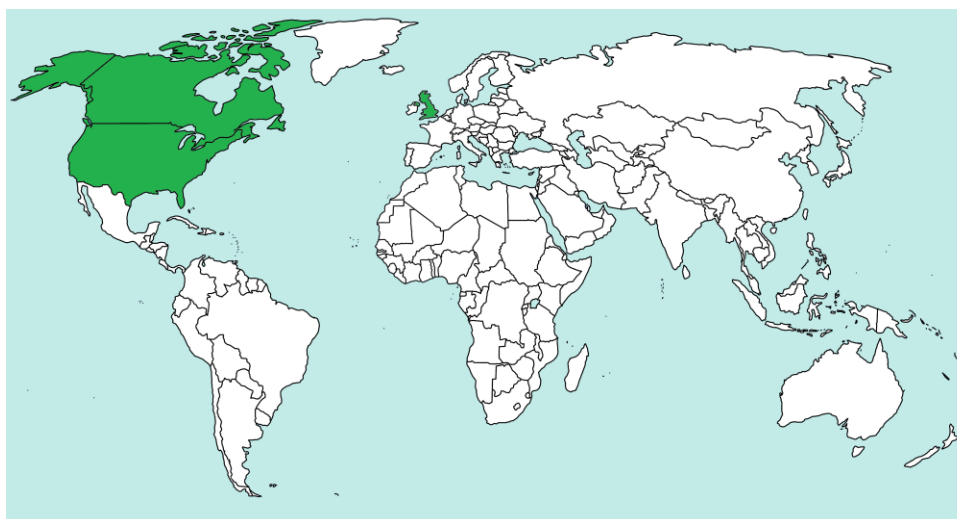
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Southampton, UK

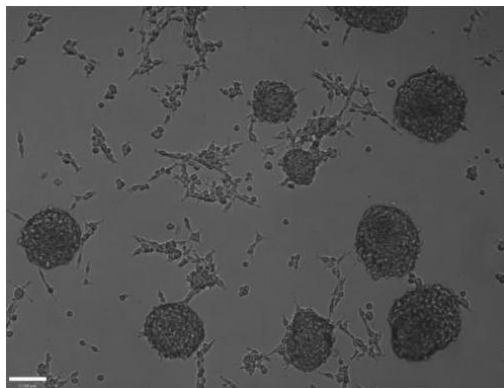
Breast Cancer Research Uncovers the Fountain of Youth

The Fountain of Youth has been discovered and it's not in Florida as Ponce de Leon claimed. Instead, it was found in the mammary glands of genetically modified mice. A research team led by Professor Rama Khokha has found that when two factors that control tissue development are removed, you can avoid the impact of aging. Think of tissue as a building that is constantly under renovation. The contractors would be "metalloproteinases," which are constantly working to demolish and reconstruct the tissue. The architects in this case, who are trying to reign in and direct the contractors, are known as "tissue inhibitors of metalloproteinases"—or TIMPs. When the architect and the contractors don't communicate well, a building can fall down. In the case of tissue, the result can be cancer. To understand how metalloproteinases and TIMPs interact, medical researchers breed mice that have one or more of the four different types of TIMPs removed. Khokha's team examined the different combinations and found that when TIMP1 and TIMP3 were removed, breast tissue remained youthful in aged mice. The results are presented in *Nature Cell Biology*. In the normal course of aging, your tissue loses its ability to develop and repair as fast as it did when you were young. That's because stem cells,

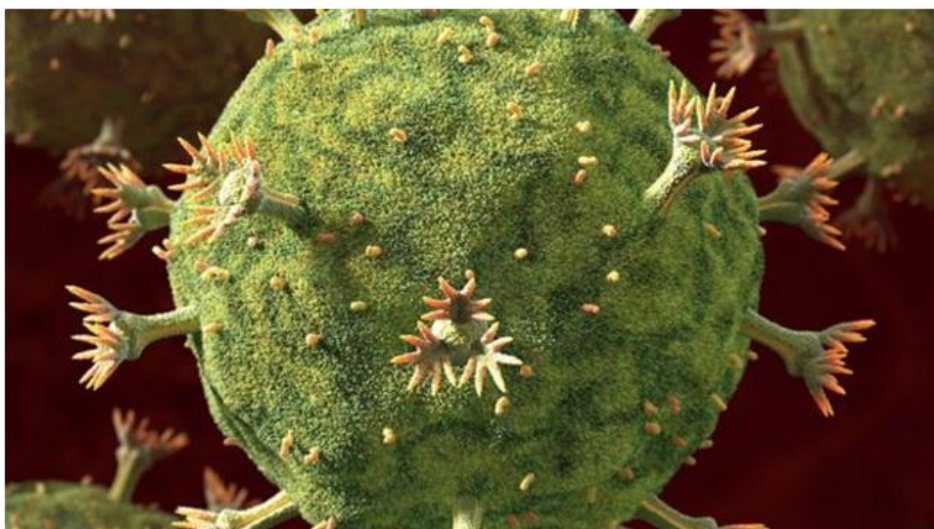


which are abundant in your youth, decline with the passing of time. The U of T team found that with the TIMP1 and TIMP3 architects missing, the pool of stem cells expanded and remained functional throughout the lifetime of these mice.

"Normally you would see these pools of stem cells, which reach their peak at six months in the mice, start to decline. As a result, the mammary glands start to degenerate, which increases the risk of breast cancer occurring," explains Khokha. "However, we found that in these particular mice, the stem cells remained consistently high when we measured them at every stage of life." The team also found that despite large number of stem cells, there was no increased risk of cancer. "It's generally assumed that the



presence of a large number of stem cells can lead to an increased cancer risk," says Khokha. "However, we found these mice had no greater predisposition to cancer." The next step in this research is to understand why this is happening. Khokha is also working with her colleagues at Princess Margaret to see how altered tissue remodeling might prevent cancer development or lead to a new therapeutic treatment for patients. Khokha is a Professor in the departments of Medical Biophysics and Laboratory Medicine and Pathobiology, as well as a Senior Scientist at the Princess Margaret Cancer Centre. Her work is supported by the Canadian Breast Cancer Foundation and the Canadian Cancer Society Research Institute. She was drawn to this research by the complexity of breast tissue. "It's a fundamental tissue that is constantly reorganizing. It develops at puberty. It goes through cycles of change in the adult female. New structures appear and regress," she explains. "It is therefore a good system to explore in order to understand tissue maintenance and



epithelial cell turnover - the cells that underlie carcinomas, the most frequent type of cancer." By Liam Mitchell. The original article was from [Phys.org](#).

Cardiff, UK

New Approach against Virus HIV

The first human trial of a new type of HIV therapy suggests it could be a promising weapon in the fight against the virus. Reports in the journal *Nature* show infusions of so-called broadly neutralising antibodies could suppress the amount of HIV in a patient's blood. The approach uses clones of immune proteins taken from a rare individual who has natural control of the disease. Scientists hope with further work this could bolster current treatments. People naturally mount a defence against the virus by producing an army of protein based weapons - antibodies. But in most cases these are not powerful enough to defeat it. The international research team harvested copies of unusually potent ones, capable of neutralising many different strains of HIV. Patients given the highest concentrations

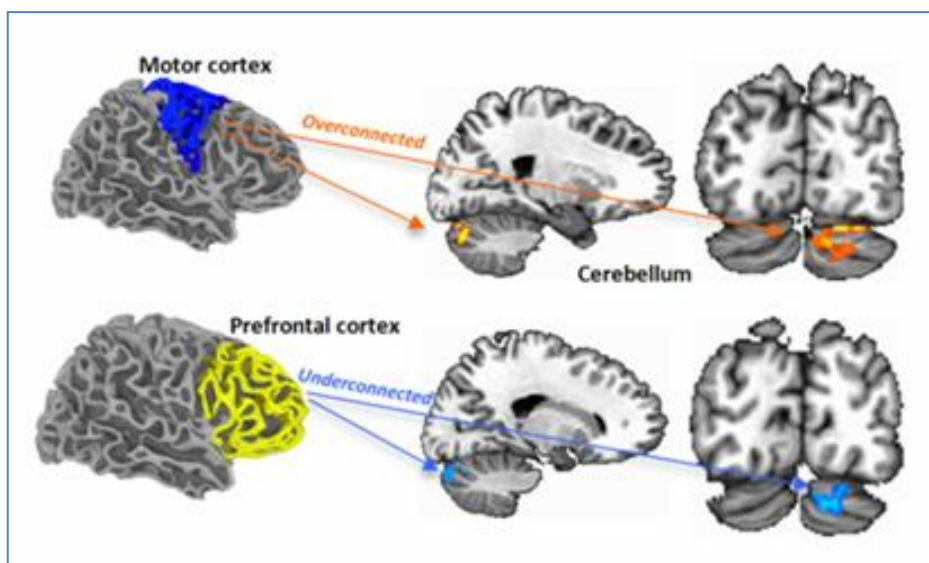
were able to fight the virus for some time, dampening the replication of HIV in their blood. The strength of this protection varied - in some it lasted more than four weeks. In the journal the authors said: "Our data establish that passive infusion of single broadly neutralising antibodies can have profound effects on HIV viraemia in humans." But because of the virus's ability to mutate rapidly, in some patients it was able to outwit the therapy by changing structure over time. To overcome this scientists suggest using this treatment alongside current drugs or together with other antibodies. Prof Michel Nussenzweig of the Rockefeller University in New York, told BBC News: "This is different to treatment out there already on two counts. "First because it comes from a human - so it is natural in that respect. "And secondly it opens up the possibility of giving the patient's own weakened immune system a jolt. "One part of the antibody could act as a red flag - pointing out to the body where the virus is hiding and sending signals to kill it." They are now exploring whether the infusion

could shield people from getting the disease in the first place. But he cautioned that studies into the antibody are still small and at an early stage. "We have shown the approach is safe and effective. "What this trial is telling us is that it is now time to look at the possibilities - from prevention and treatment to even cure," he said. Commenting on the findings, Prof Vincent Piguet from Cardiff University, said: "This exciting novel study shows for the first time that antibodies may have a place in the line of therapies directed against HIV." He described it as an "important development in the fight against HIV" but said the costs of antibody therapy and the emergence of resistance must be taken into account. By Smitha Mundasad. The original article was from the [BBC](#).

San Diego, USA

Overconnected Sensorimotor Regions of the Brain in Children with Autism

In early childhood, the neurons inside children's developing brains form connections between various regions of brain "real estate." As described in a paper published last week in the journal *Biological Psychiatry*, cognitive neuroscientists at San Diego State University found that in children and adolescents with autism spectrum disorder, the connections between the cerebral cortex and the cerebellum appear to be overdeveloped in sensorimotor regions of the brain. This overdevelopment appears to muscle in on brain "real estate" that in typi-



cally developing children is more densely occupied by connections that serve higher cognitive functioning. The study represents the first ever systematic look at connections between the entire cerebral cortex and the cerebellum using fMRI brain imaging, and its findings provide another piece in the puzzle that could one day lead researchers to develop a reliable brain-based test for identifying autism. Several decades ago, scientists reported findings that certain regions of the cerebellum—a brain region involved in motor control, but also in cognitive, social, and emotional functions—were often smaller in people with autism than in typically developing people. That sparked a brief flurry of research activity exploring the cerebellum’s potential role in the disorder. Unfortunately, the direction never truly panned out for researchers hoping for a big breakthrough in understanding, said the study’s corresponding author, SDSU psychologist Ralph-Axel Müller. “Eventually, interest in the cerebellum waned due to a lack of consistency in the findings,” he said.

Hoping that advances in brain imaging technology would reveal new insights, Müller, working with the study’s first author Amanda Khan, looked back to the cerebellum for their study. Khan is a former master’s student at SDSU and now a doctoral candidate at Suffolk University in Boston. The researchers directed 56 children and adolescents, half with autism and half without the disorder, to fixate on a focal point while thinking about nothing in particular, using fMRI brain imaging technology to scan the children’s brains as they produced spontaneous brain activity. Capturing this spontaneous activity is crucial to honing in on what are essentially baseline neuronal patterns. The imaging results revealed that the participants with autism had far stronger neuronal connectivity between sensorimotor regions of the cerebellum and cerebral cortex than did their counterparts without autism. Conversely, the participants with autism had less connectivity between regions involved in higher-order cognitive functions such as decision-making, attention and language. The sensorimotor

connections between the cerebral cortex and cerebellum mature during the first few years of life, when the brains of children with autism grow larger in volume than typically developing children, Müller explained. Connections that serve higher cognitive functions develop later, after this period of overgrowth. “Our findings suggest that the early developing sensorimotor connections are highly represented in the cerebellum at the expense of higher cognitive functions in children with autism,” he said. “By the time the higher cognitive functions begin to come online, many of the connections are already specialized. If a particular part of the brain is already functionally active in one domain, there may be no reason for the brain to switch it over to another domain later in life.” Returning to the real estate metaphor, it’s as if most of the available land has already been scooped up by sensorimotor connections before the higher-order cognitive function connections have a chance to move into the neighborhood. The findings could help scientists and clinicians better understand exactly how abnormalities during brain development lead to various types of autism spectrum disorder. Müller hopes his work will not only contribute to a brain-based diagnosis of autism, but also be a step towards identifying its various subtypes and underlying genetic factors. “We still don’t understand what in the brain makes a kid autistic,” he said. “You can’t look at a scan and say, ‘There it is.’ We’re doing the groundwork of finding brain variables that

might be biomarkers for autism and its subtypes.” The original article from the [NEUROSCIENCE NEWS](#).

Ann Arbor, USA

Using Forks and Knives Has Changed the Human Face

From the time we're born to when we're old and grey, the food we eat plays a major role in how we look and feel. It's not just our daily dietary habits, though. The way our ancestors began eating their food hundreds of years ago has a lot to do with how the human face looks today, and not in a good way. One example is the overbite, which is a common dental abnormality that developed relatively recently in human history. Before 250 years ago, Europeans were overbite-free. American anthropologist Charles Loring Brace at the University of Michigan thinks this had much to do with how and what they were eating. That was a revelation that took an important discovery, though. For most of his career, Brace thought, like many other scientists in his field, that the overbite was the result of a gradual, evolutionary change in human jaw size that began at the dawn of agriculture, around 12,000 years ago. But all of that changed when Brace learned, in 1977, that the Chinese population developed the overbite 900 years before the Europeans. He discovered this by comparing Chinese skulls that exhibited an overbite with the oldest known European skulls with the same dental abnormali-



ty, and the discrepancy in the age of the skulls, 900 years, was a surprise. Brace also knew that the Chinese began using chopsticks 900 years before Europeans took up the knife and fork. The difference between the age of the overbite and the advent of utensils between the two cultures could not be ignored. The most logical explanation, which still stands today, that Brace found was that the overbite was a relatively quick change in the human jaw not because of evolution but because of lazy eating brought on by silverware. Ancient Europeans chowed down raw fruits and vegetables and ripped meat from bone with their hands. But around 250 years ago, they picked up the fork and knife and began eating smaller, bite-sized foods, which put less strain and stress on their jaw muscles. The muscles in our jaws need exercise like any other muscle. Otherwise, they will weaken. This weakness, Brace concluded, is what leads to overbites. Furthermore, Brace concluded that the over-

bite was not a gradual evolutionary trait at all but an abrupt change brought on by how we use our teeth and jaw muscles. Brace's conclusions were a shock to some. "The first time I read Brace's work, I was truly astonished" Bee Wilson, a British food writer and historian, told *The Atlantic*. "So often, we assume that the tools we use for eating are more or less irrelevant — at most, a question of manners. I found it remarkable that they could have this graphic impact on the human body." Brace's hypothesis has since been corroborated with other studies. In the early 2000s, a team of scientists at Harvard did an experiment on baby rock badgers. Some of the animals were fed raw and dried foods while others were on a strict diet of soft, cooked foods. They found that the rock badgers raised on cooked food had approximately 10% less growth in their upper and lower jaws than the badgers eating the raw, dried food. The scientists reported their findings in the *Journal Human Evolutions*.

So, the next time you're at the dentist, reading that crappy, old magazine, dreading whatever work you are about to have done, you're well within your right to blame your parents for cooking you hot meals and making you cut your food into bite-sized pieces to eat with silverware. By Jessica Orwig. The original article from [YAHOO](#).

Cambridge, UK

Human DNA Features Genes from Plants, Microorganisms

Genes will regularly jump ship, linking up with another organism, if given the chance. It's a process known as horizontal gene transfer. But previously, scientists believed this was mostly a strategy of smaller organisms. A new study, however, suggests natural transgenics is equally common among larger species like humans. In fact, it's now clear that humans regularly swap genes with the germs they host and the plants they eat. "This is the first study to show how widely horizontal gene transfer occurs in animals, including humans, giving rise to tens or hundreds of active 'foreign' genes," explained lead author Alastair Crisp, a researcher in chemical engineering and biotechnology at the University of Cambridge. "Surprisingly, far from being a rare occurrence, it appears that this has contributed to the evolution of many, perhaps all, animals and that the process is ongoing," Crisp said. "We may need to re-evaluate how we think about evolution." Researchers analyzed the genomes of sev-

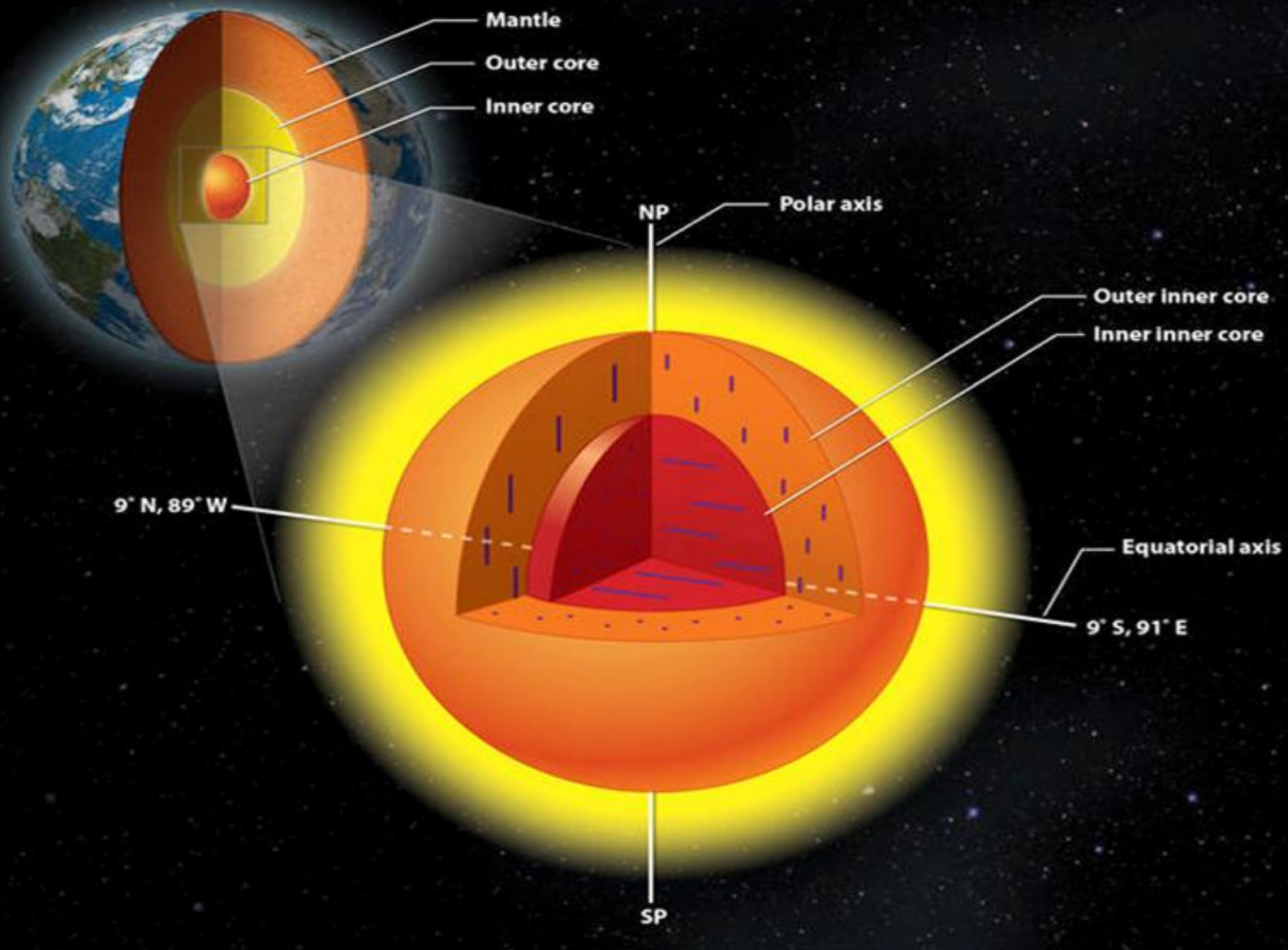


eral dozen species, including several types of fruit fly, nematode worm, and primate, including humans. After comparing genomes of similar species, scientists were able to isolate genes most likely to have come from foreign origins. Scientists found at least 145 genes likely to have been acquired via horizontal gene transfer, only 17 of which had been previously identified. Many of these genes are believed to be involved in metabolic processes, but many more have an undefined purpose. Bacteria and protists, a class of microorganisms, are pegged as the most frequent donors, but fungi and plants have also shared their genes readily. Researchers say it's likely their study actually underestimates natural transgenics among species. Even so, they say just one percent of the human genome is made up of transferred genes. By Brooks Hays, The original article was from the [UPI](#).

Chicago, USA

What is Going On at the Inner-Inner Core of Earth's Center

The newly discovered core at the center of the Earth has a different polarity than its surrounding core, represented by the purple lines. Though the seismic waves from earthquakes are best known for their destructive capabilities, in the hands of geologists, they can be powerful tools of discovery. A research team at the University of Illinois has just used the rumbles from quakes to more closely examine the inner core of our planet, and what they found there was quite a surprise. It seems there's another core inside the inner core that measures about half its diameter. What demarcates this "inner-inner core" is that the iron crystals it contains are oriented on an east-west axis, unlike the iron crystals in the "outer-inner core" which organize along a north-south axis. "The fact that we have two regions that are distinctly different may tell us



something about how the inner core has been evolving," Xiaodong Song, a professor of geology at UI who worked on the project with visiting postdoctoral researcher Tao Wang, said in a University of Illinois report about the findings. "For example, over the history of the Earth, the inner core might have had a very dramatic change in its deformation regime. It might hold the key to how the planet has evolved." While multiple components of the inner core have been suggested before, this is the first time the difference in polarity has been noted. "Indeed, the layering of the inner core has been suggested more than 10

years ago, at shallow depths of the inner core and at deeper parts of the inner core as well," Song told Crave. "Everyone assumed before the crystal alignment was north-south. But here we found alignment in the inner-inner core to be nearly east-west." If all this inner and inner-inner talk sounds confusing, perhaps a quick geology refresher is in order. The Earth consists of three layers: the crust where we live; the mantle, a layer of scalding-hot liquid rock; and the core. The core consists of a liquid outer core containing mainly nickel and iron and a solid inner core made up mostly of iron. Even though the inner core is even

hotter than its surroundings, the intense pressure at the Earth's center means the inner core is unable to melt and remains solid, according to a National Geographic entry about the topic. And now we can add another layer to our Earth's composition: the inner-inner core, which is still mostly solid iron, but has a different polarity than the substance surrounding it. In "unearthing" the inner-inner core, the research team relied on seismic sensors that pick up the waves that penetrate the planet after an earthquake hits, known as the quake's coda. "The earthquake is like a hammer striking a bell; much like a listener hears the clear tone that

resonates after the bell strike, seismic sensors collect a coherent signal in the earthquake's coda," the report says. "It turns out the coherent signal enhanced by the technology is clearer than the ring itself," said Song. "The basic idea of the method has been around for a while, and people have used it for other kinds of studies near the surface. But we are looking all the way through the center of the Earth." By Michael Franco, the original article was from [CNET](#).

Edmonton, CANADA

50-Foot-Long 'Dragon' Dinosaur Species Discovered In China

The long-necked Qijianglong lived about 160 million years ago in the Late Jurassic period. Sauropods, a category of dinosaurs that includes the Diplodocus, typically had necks that comprised up to a third of their body size. A new species of dinosaur described in a recent *Journal of Vertebrate Paleontology* had a neck that could stretch up to 25 feet long, which is half its body length. The dino has been named Qijianglong (pronounced "CHI-jyang-lon"), which means "dragon of Qijiang." Its bones were discovered near China's Qijiang City by construction workers in 2006. It belongs to a family of sauropods known as mamenchisaurids. Miraculously, when the beast was unearthed, its head was still attached to its vertebrae, something extremely unusual in the paleontology world. "It is rare to find a head



and neck of a long-necked dinosaur together because the head is so small and easily detached after the animal dies," explains Tetsuto Miyashita, a University of Alberta paleontologist who, along with former master's student Lida Xing and professor Philip Currie, discovered the new species. Also of note is that the dinosaur's vertebrae were filled with air, much like the skeletons of birds. This made their necks fairly lightweight for their massive size (and no doubt, kept them from face-planting when they were being chased by other big bad-dies). The vertebrae were also found to be interlocking in such a way that would have allowed the dinosaur to lift its head up and down like a construction crane, but not move it very easily from side to side. The dragon of Qijiang is thought to have lived about 160 million years ago during the Late Jurassic period, when dinosaurs like the Stegosaurus also roamed Earth. Its unusually long neck hints at the breadth of evolutionary adaptations, says Miyashita. "Qijianglong is

a cool animal. If you imagine a big animal that is half neck, you can see that evolution can do quite extraordinary things," he said in a statement. The paleontologist also wonders if ancient residents of China -- the only place where mamenchisaurids are found -- once stumbled upon the remains of a Qijianglong, which could have contributed to legends of dragons in the region. "China is home to the ancient myths of dragons," said Miyashita. "I wonder if the ancient Chinese stumbled upon a skeleton of a long-necked dinosaur like Qijianglong and pictured that mythical creature." by Michael Franco, the original article was from [UOFA](#).

Edmonton, CANADA

Oldest Snake Fossils Show They Thrived In the Age of Dinosaurs

Researchers have unearthed the fossil remains of four snakes that are 70 million years older than the oldest snake previously discovered. The



finds rewrite what scientists know about the creatures, showing that they were slithering alongside pterodactyls and other dinosaurs as early 167 million years ago. "We've nearly doubled the geological range for a group," said Michael Caldwell, a professor in the Faculty of Science at the University of Alberta, and lead au-

thor of a new study in *Nature Communications*. Not only do his findings offer clues on how these reptiles may have evolved, they also reveal that the snakes of the dinosaur age probably didn't look all that different than their modern-day relatives. Though dating from 140 million to 167 million years ago, the fossilized skulls, jaws, ribs and teeth share many fea-

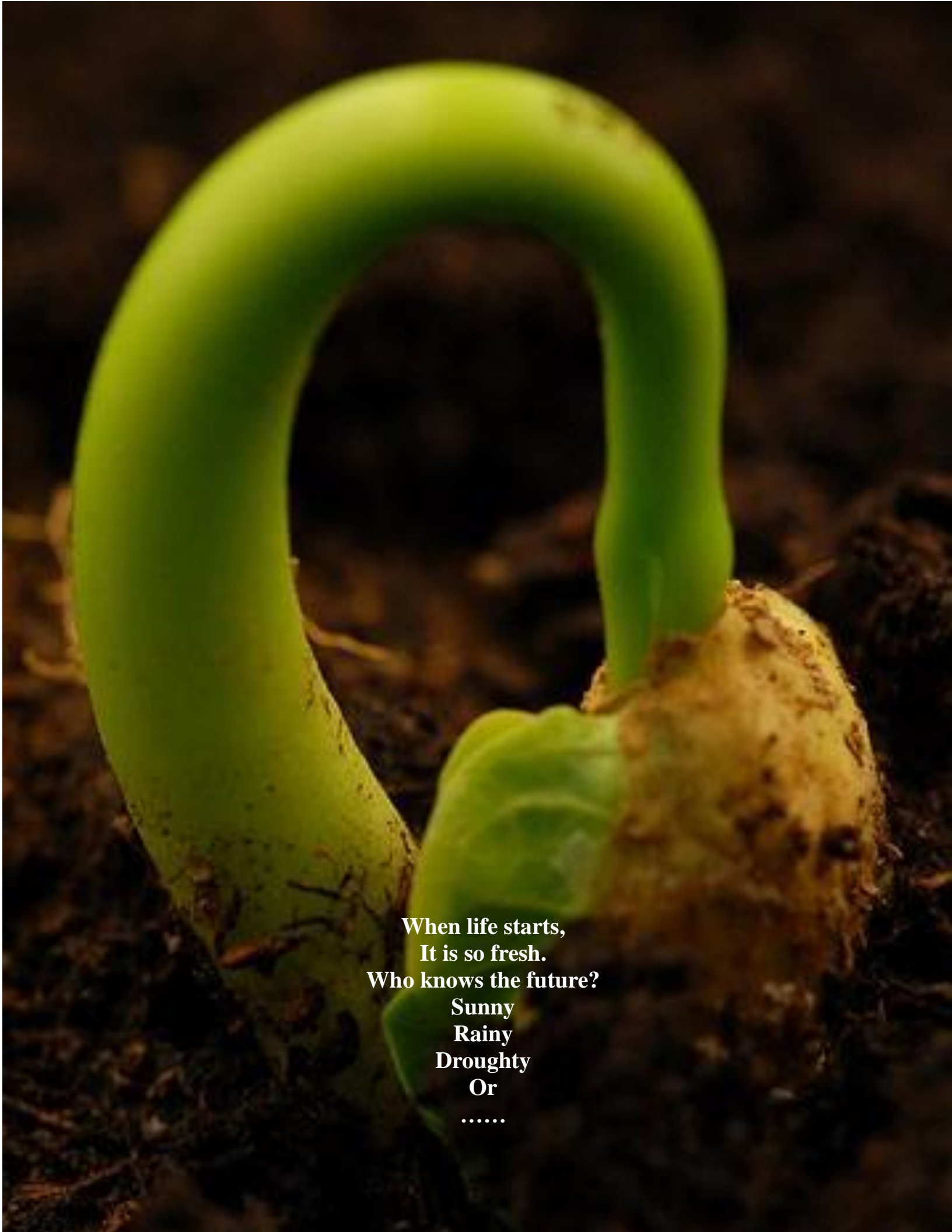
tures seen in today's snakes, such as the flexible jaws and sharply-angled, backward-pointing teeth which are instrumental in helping them devour their prey. They also have features found in lizards such as its vertebrae. Caldwell said he was surprised snakes had changed so little over such a long period of time and that they were still so clear-



ly "identifiable ... as snakes." Normally you would expect to dig up something that shared traits with modern animals, but looked different, perhaps more like some sort of chimera of two familiar beasts, he said. "You know like the bird-dinosaur idea. You wouldn't be looking for a modern duck in the middle of the Cretaceous." The oldest of the fossils (the diminutive *Eophis underwoodi*) came from southern England. The largest, *Portugalophis lignites*, came from coal deposits in Portugal, and was a much bigger individual at nearly a meter or more in length. Around 150 million years ago, the locations in England and Portugal were swampy coastal areas on large island chains in the Jurassic seaway that covered most of what is now Western and Central Europe. The one North American species identified, *Diablophis gilmorei*, was found in river deposits in Western Colorado. The locations offer evidence that the snakes came from a marine environment. "Is it possible, like a lot of other animals today, they moved around the planet by swimming? Yep, it's very possible. Almost all modern snakes are perfectly

comfortable in the water," Caldwell said. Caldwell also believes these snakes probably had four limbs - though there aren't the fossils to prove it. An earlier discovery from Caldwell and his colleagues turned up 100- to 90-million-year-old marine snakes from the West Bank, Lebanon, and Argentina that still possessed small but well developed rear limbs. They also varied in size: A snake fossil from 60 million years ago called *Titanoboa* was probably about 10 times bigger than snakes today. "It could very well be that what you would see in terms of the missing link features is that this animal would have had four legs and a short body," Caldwell said. "Body-wise, it wouldn't have looked like a modern snake but the skull is clearly demonstrating very snaky features." Caldwell said the latest discoveries probably aren't going to settle a long-running debate about how snakes evolved. Some said they evolved from burrowing animals - based on primitive, blind snakes alive today that live in burrows - while Caldwell and his supporters have argue they evolved from four-legged, lizard-like ancestors that thrived in the oceans

and emerged onto land. "I suspect we will never put that debate to rest," he said. "It's a very fine scale question and an interesting one ... We have an anatomical and a relationship problem and then we have to find that point in time in the fossil record where we would actually recognize one of these animals as a snake ... If I can find you a four-legged animal with a snake head, will you call it a snake or will we call it a snake-like lizard?" To really shore up the theory, researchers need a snake fossil further back that has four legs which could take snake evolution to 200 million years. They also need to shore up the fossil record from 167 million to 100 million years ago. That means expanding the area they have searched for snake fossils. Since the latest crop of fossils came from the Northern Hemisphere and what was then the supercontinent Laurasia, researchers will go in search of fossils in the southern Hemisphere in South America, Africa and Australia or what was then Gondwana. "We are trying to fill in those bits and pieces of the story," Caldwell said. The original article was from [CBS](#).

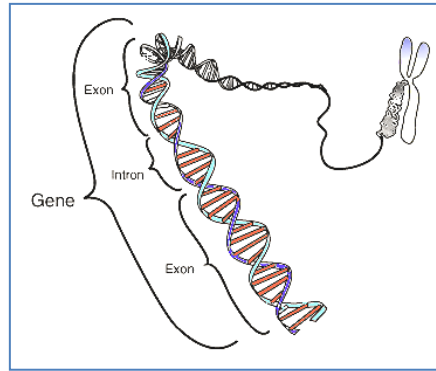
A young green plant with a curved stem and a root ball, growing in dark soil. The stem is bright green and arches over, forming a loop. The root ball is light brown and textured. The background is dark and out of focus.

**When life starts,
It is so fresh.
Who knows the future?
Sunny
Rainy
Droughty
Or
.....**

BIOLOGY, CANADA

Organisms Can Keep Gene Expression in Check

York University researchers have learned how living beings can keep gene expression in check—which might partly explain the uncontrolled gene expression found in many cancers. "Using yeast as a model organism, we studied the Tup1 protein, a negative regulator of gene expression," says Biology Professor Emanuel Rosonina, adding, "This protein binds to some genes and blocks their expression, helping to ensure genes that shouldn't be turned on remain inactive." The current study, jointly conducted by York University and Columbia University researchers, suggests that Small Ubiquitin-like Modifier (SUMO) modifies proteins bound to active genes, in order to prevent unfettered gene over-expression that can be harmful to the organism. "One of the ways SUMO does this is by promoting the binding of Tup1 to active genes, which then acts to reduce their expression to appropriate levels," explains Rosonina, in the Faculty of Science at York U. "Sumoylation controls the timing of Tup1-mediated transcriptional deactivation" published in *Nature Communications* is a follow up to a previous study which found SUMO in every gene examined. "As a result of the previous study, we reported that SUMO is probably important for controlling expression of active genes because we found it on every gene we looked at, but only when they were turned on," notes Rosonina. Considering that many tumours have abnormal levels of SUMO, it will be important to examine whether inappropriate SUMO modifications in these tumours



are related to the uncontrolled gene expression that is observed in most cancers, the research concludes.

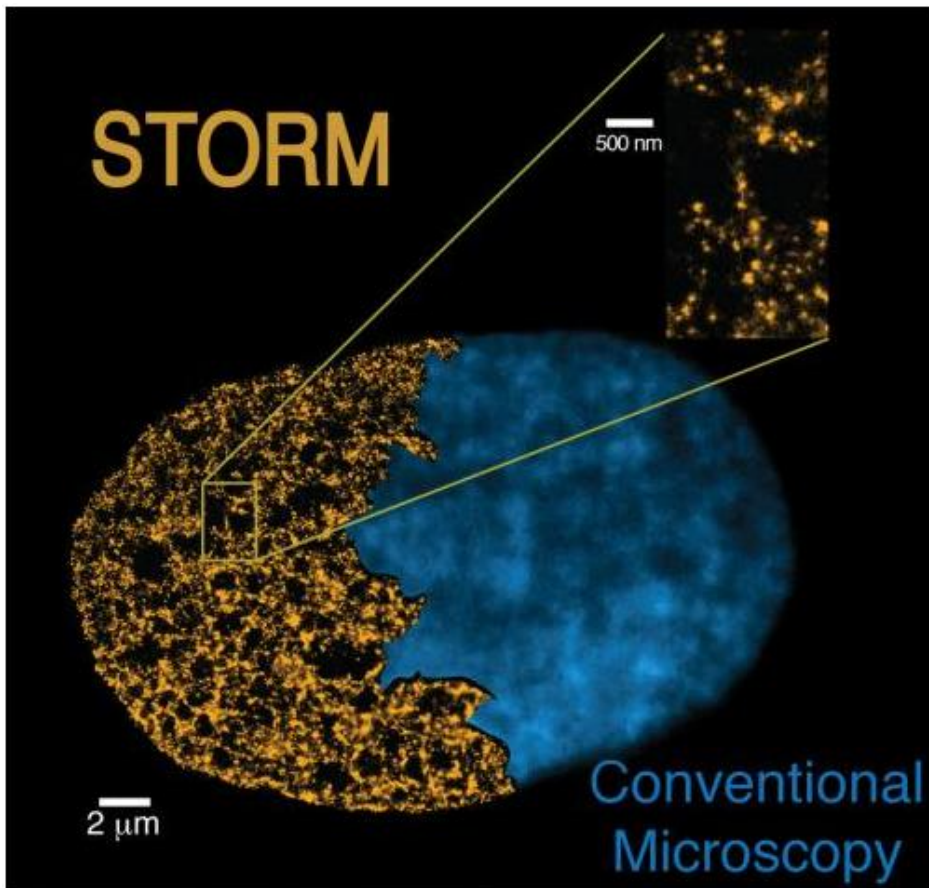
Nature Communications 2015;
Doi: 10.1038/ncomms7610

CELL BIOLOGY, SPAIN

The Link between Genome Packaging and Cell Pluripotency

A study using Super-resolution microscopy reveals that our genome is not regularly packaged and links these packaging differences to stem cell state. A multi-disciplinary approach allowed scientists to view and even count, for the first time, the smallest units for packaging our genome. This study has brought together biologists and physicists from the Centre for Genomic Regulation and the Institute of Photonic Sciences, both in Barcelona. In 1953 Watson and Crick first published the discovery of the double helix structure of the DNA. They were able to visualize the DNA structure by means of X-Ray diffraction. Techniques, such as electron microscopy, allowed scientists to identify nucleosomes, the first and most basic level of chromosome organisation. Until now it was known that our DNA is packaged by regular repeating units of those nucleosomes throughout the genome giving rise to chro-

matin. However, due to the lack of suitable techniques and instruments, the chromatin organisation inside a cell nucleus could not be observed in a non-invasive way with the sufficient resolution. Now, for the first time, a group of scientists at the CRG and ICFO in Barcelona, have been able to visualise and even count the smallest units which, packaged together, form our genome. This study was possible thanks to the use of super-resolution microscopy, a new cutting-edge optical technique that received the Nobel Prize in Chemistry in 2014. In combination with innovative quantitative approaches and numerical simulations, they were also able to define the genome architecture at the nano-scale. Most importantly, they found that the nucleosomes are assembled in irregular groups across the chromatin and nucleosome-free-DNA regions separate these groups. Biologists and physicists have been working together to take a step forward in chromatin fibre observations and studies. "By using the STORM technique, a new super-resolution microscopy method, we have been able to view and even count nucleosomes across the chromatin fibers and determine their organisation. STORM overcomes the diffraction limit that normally restricts the spatial resolution of conventional microscopes and enables us to precisely define the chromatin fibre structure", states Prof. Melike Lakadamyali, group leader at ICFO. This enabling technique allowed the researchers to go deeper and, by comparing stem cells to differentiated cells (specialised cells that have already acquired their role), they observed key differences in the chromatin fibre architectures of both cells. Pia Cosma, group leader and ICREA



research professor at the CRG explains, "We found that stem cells have a different chromatin structure than somatic (specialised) cells. At the same time, this difference correlates with the level of pluripotency. The more pluripotent a cell is, the less dense is its packaging. It gives us new clues to understand the stem cells functioning and their genomic structure, which will be helpful for example, in studying cell reprogramming". What scientists have found is that DNA is not regularly packaged with nucleosomes, instead nucleosomes are assembled in groups of varying sizes, called "nucleosome clutches" -because of their similarity to egg clutches-. They found that pluripotent stem cells have, on average, clutches with less density of nucleosomes. In addition, clutch size is related to the pluripotency potential of stem cells, meaning that the more pluripotent a cell is, the less nucleosomes are included in

its clutches. Even though all the cells in our body have the same genetic information, they are not expressing all the genes at the same time. So, when a cell specialises, some of the DNA regions are silenced or less accessible to the molecule that reads the genome: the RNA polymerase. Depending on the specialisation of the cells, different levels of DNA packaging will occur. This new work published in the prestigious journal *Cell*, establishes a new understanding of how the chromatin fibre is assembled and packaged forming a specific DNA structure in every cell. This research definitively contributes to the understanding of a novel feature of stem cells and their DNA structure, which is important for maintaining an induced pluripotent state. A joint patent has been filed by ICFO and CRG, who are now exploring business opportunities for marketing the classification of "stemness" state of cells, ie, their

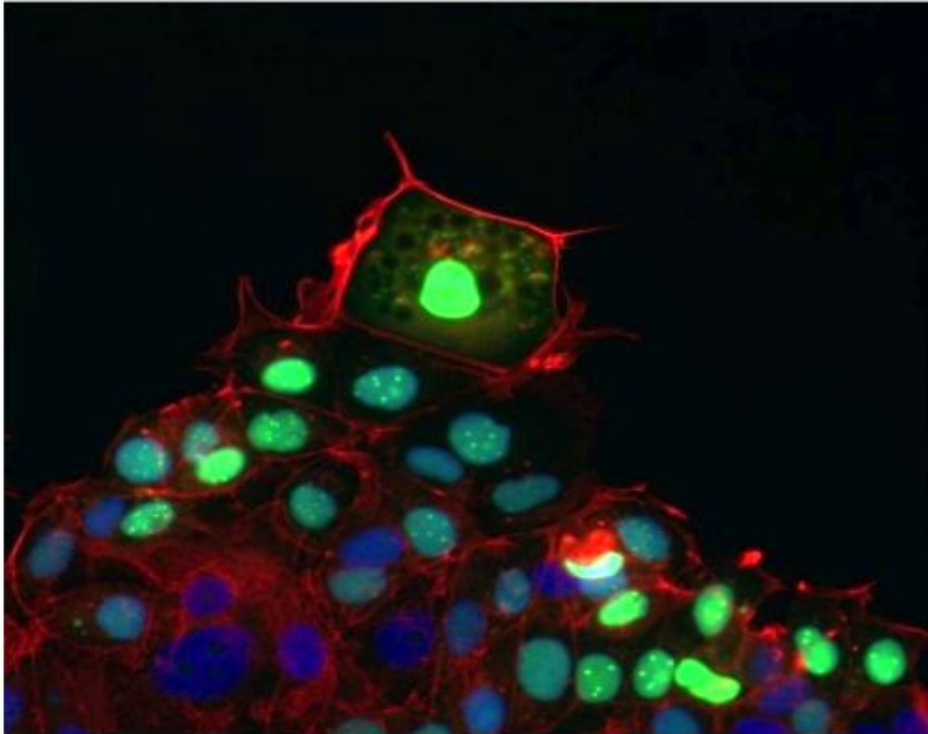
degree of pluripotency. This technique could determine with single cell sensitivity the pluripotency potential of stem cells, thus having the capacity of becoming a standard method of quality control of stem or pluripotent cells before their use in cell therapy or research in biomedicine.

Cell 2015; Doi:
10.1016/j.cell.2015.01.054

MEDICINE, USA

The Mysteries of Wound Healing

Researchers at the University of Arizona have discovered what causes and regulates collective cell migration, one of the most universal but least understood biological processes in all living organisms. The findings, published in the March 13, 2015, edition of *Nature Communications*, shed light on the mechanisms of cell migration, particularly in the wound-healing process. The results represent a major advancement for regenerative medicine, in which biomedical engineers and other researchers manipulate cells' form and function to create new tissues, and even organs, to repair, restore or replace those damaged by injury or disease. "The results significantly increase our understanding of how tissue regeneration is regulated and advance our ability to guide these processes," said Pak Kin Wong, UA associate professor of mechanical and aerospace engineering and lead investigator of the research. "In recent years, researchers have gained a better understanding of the molecular machinery of cell migration, but not what directs it to happen in the first place," he said. "What, exactly, is orchestrating this system common to all living organisms?" The answer, it turns out, involves delicate interactions be-



tween biomechanical stress, or force, which living cells exert on one another, and biochemical signaling. The UA researchers discovered that when mechanical force disappears—for example at a wound site where cells have been destroyed, leaving empty, cell-free space—a protein molecule, known as Dll4, coordinates nearby cells to migrate to a wound site and collectively cover it with new tissue. What's more, they found, this process causes identical cells to specialize into leader and follower cells. Researchers had previously assumed leader cells formed randomly. Wong's team observed that when cells collectively migrate toward a wound, leader cells expressing a form of messenger RNA, or mRNA, genetic code specific to the Dll4 protein emerge at the front of the pack, or migrating tip. The leader cells, in turn, send signals to follower cells, which do not express the genetic messenger. This elaborate autoregulatory system remains activated until new tissue has covered a wound. The same migration processes for wound healing and tissue development

also apply to cancer spreading, the researchers noted. The combination of mechanical force and genetic signaling stimulates cancer cells to collectively migrate and invade healthy tissue. Biologists have known of the existence of leader cells and the Dll4 protein for some years and have suspected they might be important in collective cell migration. But precisely how leader cells formed, what controlled their behavior, and their genetic makeup were all mysteries—until now. "Knowing the genetic makeup of leader cells and understanding their formation and behavior gives us the ability to alter cell migration," Wong said. With this new knowledge, researchers can re-create, at the cellular and molecular levels, the chain of events that brings about the formation of human tissue. Bioengineers now have the information they need to direct normal cells to heal damaged tissue, or prevent cancer cells from invading healthy tissue. The UA team's findings have major implications for people with a variety of diseases and conditions. For example, the discover-

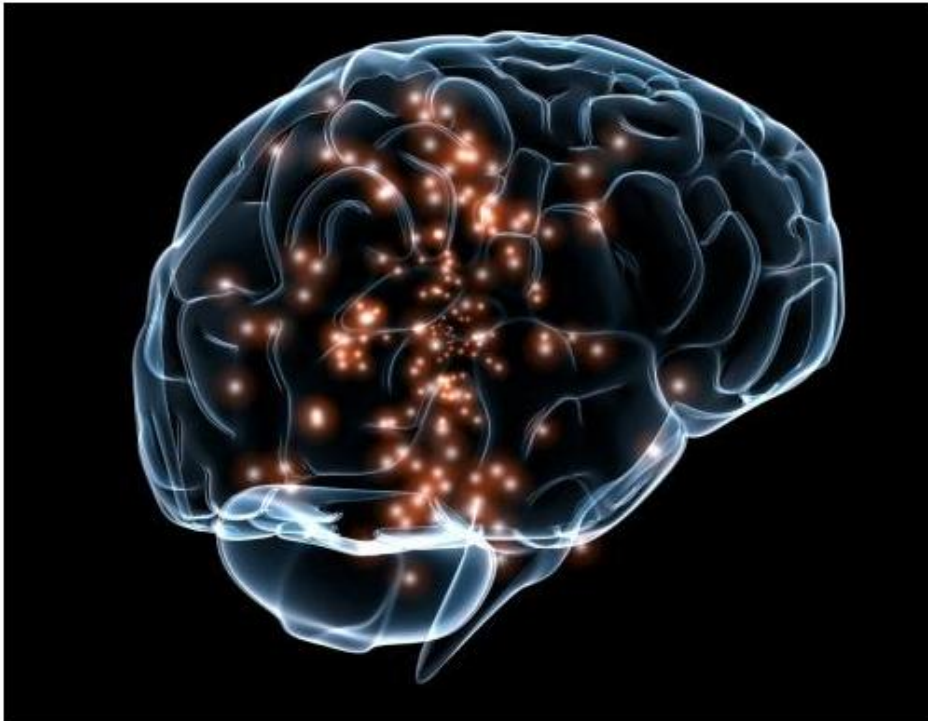
ies may lead to better treatments for non-healing diabetic wounds, the No. 1 cause of lower limb amputations in the United States; for plaque buildup in arteries, a major cause of heart disease; and for slowing or even stopping the spread of cancer, which is what makes it so deadly. The research also has the potential to speed up development of bioengineered tissues and organs that can be successfully transplanted in humans.

Nature Communications 2015;
Doi: [10.1038/ncomms7556](https://doi.org/10.1038/ncomms7556)

NEUROSCIENCE, FINLAND

Classical Music Modulates Genes That are Responsible for Brain Functions

Although listening to music is common in all societies, the biological determinants of listening to music are largely unknown. According to a latest study, listening to classical music enhanced the activity of genes involved in dopamine secretion and transport, synaptic neurotransmission, learning and memory, and down-regulated the genes mediating neurodegeneration. Several of the up-regulated genes were known to be responsible for song learning and singing in songbirds, suggesting a common evolutionary background of sound perception across species. Listening to music represents a complex cognitive function of the human brain, which is known to induce several neuronal and physiological changes. However, the molecular background underlying the effects of listening to music is largely unknown. A Finnish study group has investigated how listening to classical music affected the gene expression profiles of



both musically experienced and inexperienced participants. All the participants listened to W.A. Mozart's violin concert Nr 3, G-major, K.216 that lasts 20 minutes. Listening to music enhanced the activity of genes involved in dopamine secretion and transport, synaptic function, learning and memory. One of the most up-regulated genes, synuclein-alpha (SNCA) is a known risk gene for Parkinson's disease that is located in the strongest linkage region of musical aptitude. SNCA is also known to contribute to song learning in songbirds. "The up-regulation of several genes that are known to be responsible for song learning and singing in songbirds suggest a shared evolutionary background of sound perception between vocalizing birds and humans", says Dr. Irma Järvelä, the leader of the study. In contrast, listening to music down-regulated genes that are associated with neurodegeneration, referring to a neuroprotective role of music. "The effect was only detectable in musically experienced participants, suggesting the importance

of familiarity and experience in mediating music-induced effects", researchers remark. The findings give new information about the molecular genetic background of music perception and evolution, and may give further insights about the molecular mechanisms underlying music therapy.

PeerJ 2015; Doi:
10.7717/peerj.830

PLANT, SWITZERLAND

Antibiotics Have Unexpected Effects on Mitochondria

An EPFL study has shown that tetracycline-based antibiotics have an unexpected effect on the development of many organisms. In addition to pointing out the issue of soil pollution by these antibiotics, which are widely administered to livestock, the scientists call upon colleagues to explore the consequences of using them in experiments that modulate gene expression. No one assumes that antibiotics are completely harmless. But a new study shows that some of them have unexpected consequences

on the development of a wide variety of organisms. Scientists have observed significant effects in concentrations similar to those found in the soils in which our food crops are grown. Since the discovery of penicillin in the first half of the 20th century, antibiotics have been a boon to medicine for their effectiveness in combating bacterial infection. Over the past few decades, the use of new generations of drugs based on specific molecules known as tetracyclines has become very widespread. They act on bacterial gene expression, weakening, stimulating, or shutting it down altogether. This ability to act directly at the level of gene expression has also led many scientists to

use tetracycline antibiotics in research. But a study done at Ecole polytechnique fédérale de Lausanne (EPFL, Switzerland), published today in the scientific journal *Cell Reports*, calls for caution when using this family of antibiotics. The scientists, led by Norman Moullan and Laurent Mouchiroud from EPFL's Laboratory of Integrative and Systemic Physiology (Nestlé Chair in Energy Metabolism), directed by Professor Johan Auwerx, observed that these molecules have a significant effect on mitochondria, the cell's "powerhouses." "It's not that surprising, given that mitochondria are historically bacteria that evolved within our cells," says Mouchiroud. "A lot of attention has been paid to the role of antibiotics on our intestinal flora, which has ten times more cells than the rest of our bodies. However, the effects of antibiotics on our mitochondria, which themselves far outnumber the bacteria in our gut, haven't yet been studied in detail." In collaboration with two other research teams, one Swiss (Bart DePlancke) and one Dutch (Riekelt Houtkooper), the EPFL



scientists revisited data from previous studies from this angle and carried out new experiments using animal and plant cells. The effects were huge. "After several days of treatment with high doses of doxycycline, mitochondrial respiration was visibly altered," explains Moullan. More surprising still, the consequences were observed all the way down the food chain, from mammals to flies to nematode worms to plants. "The worms' development was hindered. On the other hand, signs of aging appeared more slowly, something we had observed in earlier studies." The scientists also carried out growth tests on *Arabidopsis thaliana*, a common plant that's frequently used in laboratory research. After growing for a week on a normal substrate, it was transplanted into soil with varying concentrations of doxycycline. "Delays in growth, some quite severe, were observed after a few days, even in soils in which the concentration of antibiotics was no stronger than is found in some agricultural soils today," says Moullan. This pollution whose consequences are just beginning to be appreciated is caused by the widespread administration of antibiotics to livestock. "Because they are given orally in feed, they are only partially digested and end up in manure, which is then

spread on the fields," explains Mouchiroud. The quantities involved are huge, and the economic stakes equally sobering. In 2011, 5.6 million kg of tetracycline was administered to US livestock. A study showed that nearly half of the 210 kg of antibiotics produced in China in 2007 were tetracyclines for veterinary use. "The effects on growth of plants other than *A. thaliana* have not yet been studied, but our work indicates a need for caution," says Moullan. The researchers also call on their scientific colleagues to be more careful when using antibiotics in experiments for modulating gene expression. "You observe the effect you're looking for, but you lose sight of the fact that these substances have serious consequences for overall metabolic function," says

Cell Reports 2015; Doi: 10.1016/j.celrep.2015.02.034

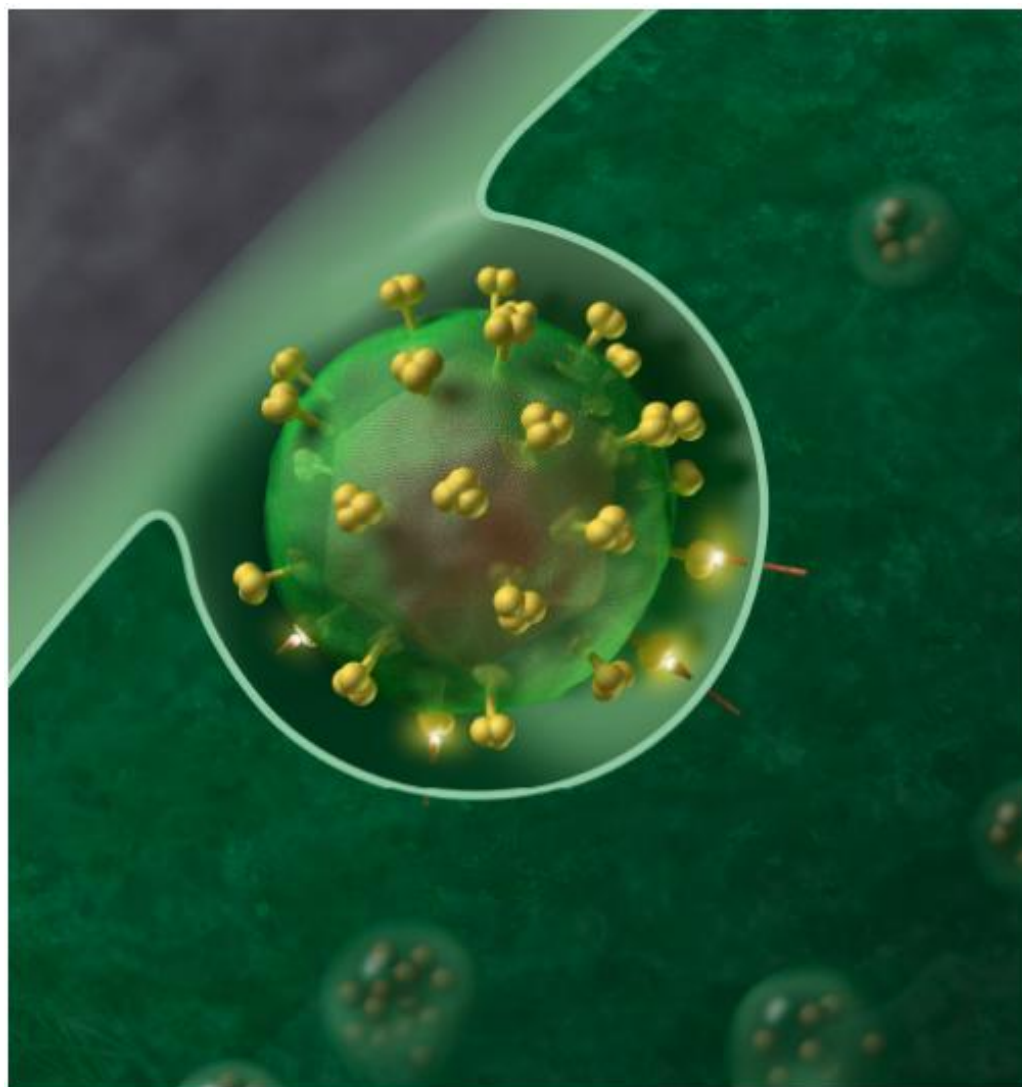
MEDICINE, USA

Common Herpes Medication Reduces HIV-1 Levels

Case Western Reserve researchers are part of an international team that has discovered that a common herpes drug reduces HIV-1 levels—even when patients do not have herpes.

Published online in *Clinical Infectious Diseases*, the finding rebuts earlier scientific assumptions that Valacyclovir (brand name, Valtrex) required the presence of the other infection to benefit patients with HIV-1. The result not only means that Valacyclovir can be used effectively with a broader range of HIV-1 patients, but also suggests promising new avenues for the development of HIV-fighting drugs. This insight is particularly significant given that some forms of HIV-1 have become resistant to existing medications. "These results demonstrated that the mechanism by which Valacyclovir acts against HIV is not only through the presence of HSV-2," said senior author Benigno Rodriguez, MD, associate professor of medicine and infectious diseases, CWRU School of Medicine, co-Principal Investigator, Case Western Reserve University/University Hospitals Case Medical Center AIDS Clinical Trials Unit, and infectious disease specialist with UH Case Medical Center. Even better, Rodriguez said, studies by these groups helped illuminate exactly how the medication decreases HIV-1 levels. Valacyclovir is activated in virus-infected cells, and then blocks the ability of HIV to reproduce. The result? Reduced viral load. HIV-1 can lead to the immune deficiency known as AIDS. The herpes simplex virus 2 (HSV-2) causes periodic recurrence of genital herpes lesions, which increase the likelihood that a herpes sufferer may contract HIV through intimate contact. HSV-2 outbreaks are treated with either Acyclovir or the newer generation Valacyclovir, which requires less frequent dosing. Scientists previously thought that Valacyclovir helped reduce HIV levels and worked by decreasing the immune activation caused by HSV-2. With fewer immune cells to

attack, the theory went, HIV-1 could not spread as widely. Yet Leonid Margolis, PhD, of the National Institutes of Health (NIH), believed another explanation might exist. After conducting laboratory studies with Acyclovir, an earlier sibling drug of Valacyclovir, Margolis saw that the medication clearly blocked HIV-1 reproduction, even when HSV-2 was absent. Those results helped spur clinical trials of Valacyclovir in people, and Margolis is senior author of the resulting journal article. Beginning in June, 2009, patients from UH Case Medical Center and from IMPACTA, the Civic Association for Health and Education in Lima, Peru, started participating in the trials, which lasted until July, 2012. Under its protocols, half the patients took Valacyclovir twice daily for 12 weeks, while the other half took a placebo for the same period of time. After a two-week break from any medications, the two groups switched: those previously on placebo got 12 weeks of the Valacyclovir, and those who already had taken the medication now received placebos. When study participants took Valacyclovir, their HIV viral loads went down, and when they took the placebo, their HIV viral loads went up. Ultimately, a total of 18 patients participated. "Our most recent clinical study demonstrates that acyclovir blocks HIV replication directly. The anti-HIV activity of valacyclovir does not depend on blocking the inflammation caused by herpes simplex virus 2," said Michael M. Lederman, MD, also a senior author. He is the Scott R. Inkley Professor of Medicine, Case Western Reserve University School of Medicine, and Principal Investigator of the Case Western Reserve University/University Hospitals Case Medical Center AIDS Clinical Trials Unit and infectious disease



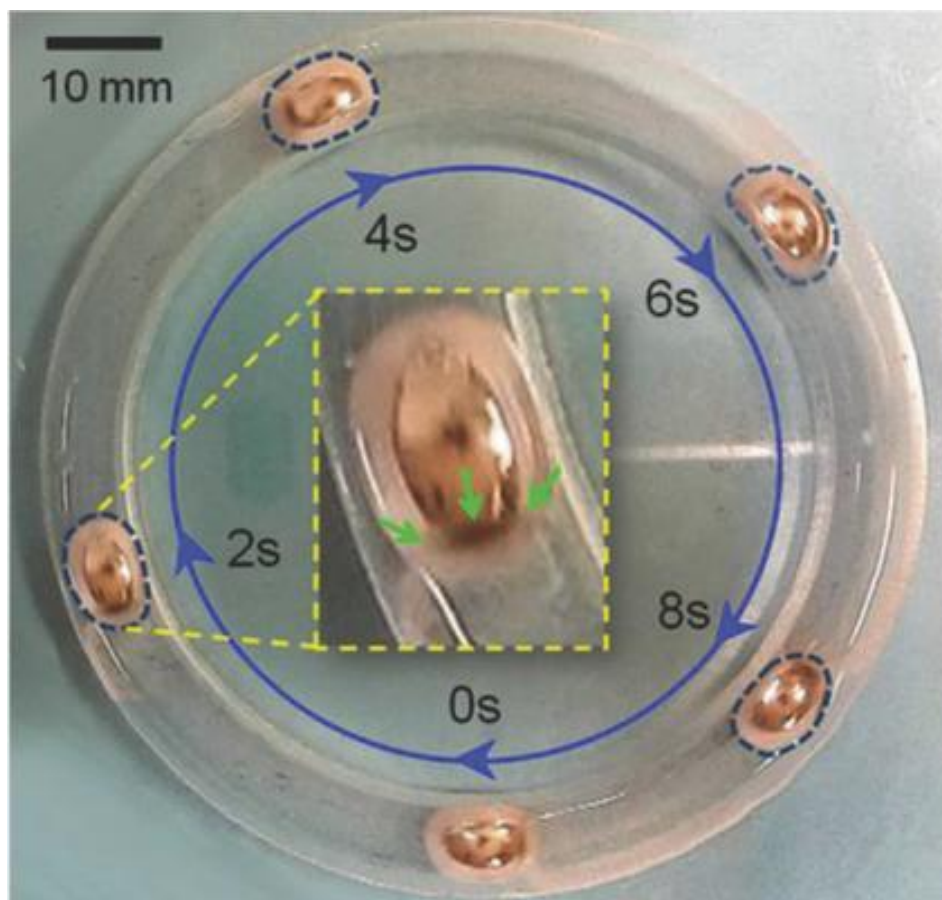
specialist with UH Case Medical Center. Lederman and Rodriguez, the two Cleveland-based members of the research team, believe that the data from this study can inform new drug development. Essentially, researchers would try to design agents based on the Valacyclovir's molecular structure - now proven to block HIV activity. "The drug might be an agent that can be used safely in some people with HIV infection who have a form of HIV that is highly resistant to other antiretroviral drugs," Lederman said. "Valacyclovir might well augment the cocktail of medications they take for reducing HIV replication. Valacyclovir is a well-tolerated drug, and it doesn't have a lot of side effects."

Clinical Infectious Diseases
2015; doi:10.1093/cid/civ172

MATERIAL, CHINA

Shape Shifting Liquid Metal Able To Propel Itself through Liquids

A team of researchers at Tsinghua University in China has, according to a report in *NewsScientist*, found a way to mimic, if only in a small way, the shape shifting robot in the *Terminator* movies. The team has published their findings in the journal *Advanced Materials*. As part of an effort to better understand the properties of liquid metals, the researchers were working with gallium—after add-



ing a little bit of indium and tin they discovered that if a bit of aluminum was affixed to a single drop of the alloy (to serve as fuel) and the result was dropped into a container of sodium hydroxide (or even salt water) the drop would propel itself around the container for approximately one hour. In subsequent tests they found that if the container was shaped with channels, the drop could be made to follow a pre-designated path. What's more, they noted that if the drop encountered a part of the channel that was slimmer than it was, it could squeeze through. Surprised by the movement of the drop, the researchers took a closer look—analysis revealed that when the drop was placed in the solution, a charge imbalance occurred between the front and back of the drop, causing a pressure differential. They also found that as the aluminum reacted with the saltwater, tiny bubbles were formed which also

served to push the drop forward (so long as the aluminum bit was on the back end.) The experiments by the team build on prior work by them and others (as part of an effort to make "soft" robots) that showed that with some liquid metals, an electric charge can cause both an expansion and change of shape to a drop. The researchers note that if both techniques were used, the result could be drops that not only move themselves through liquids, but change shape according to predetermined needs. They suggest their findings could conceivably pave the way for drops that are used to deliver materials via pipes or even through blood vessels.

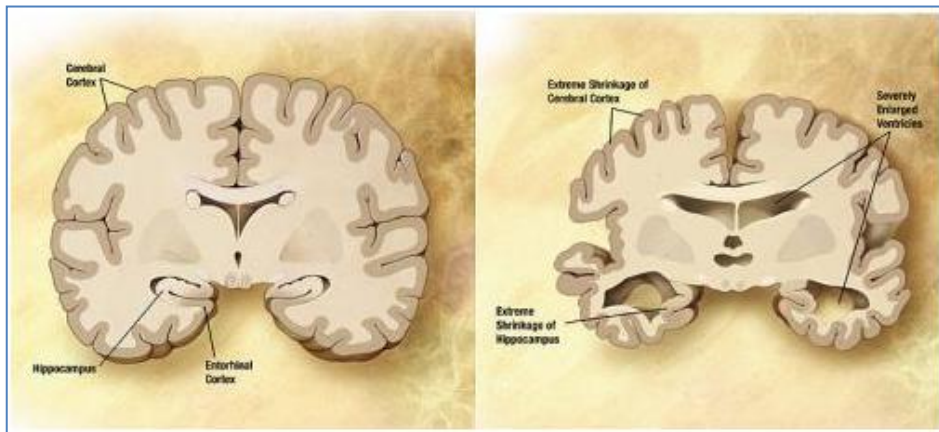
Advanced Materials 2015; Doi: 10.1002/adma.201405438

MEDICINE, USA

Drug Restores Brain Function and

Memory in Early Alzheimer's Disease

A novel therapeutic approach for an existing drug reverses a condition in elderly patients who are at high risk for dementia due to Alzheimer's disease, researchers at Johns Hopkins University found. The drug, commonly used to treat epilepsy, calms hyperactivity in the brain of patients with amnesic mild cognitive impairment (aMCI), a clinically recognized condition in which memory impairment is greater than expected for a person's age and which greatly increases risk for Alzheimer's dementia, according to the study published this week in *NeuroImage: Clinical*. The findings validate the Johns Hopkins team's initial conclusions, published three years ago in the journal *Neuron*. They also closely match the results in animal studies performed by the team and scientists elsewhere. Next, neuroscientist Michela Gallagher, the lead investigator, hopes the therapy will be tested in a large-scale, longer-term clinical trial. Hippocampal over-activity is well-documented in patients with aMCI and its occurrence predicts further cognitive decline and progression to Alzheimer's dementia, Gallagher said. "What we've shown is that very low doses of the atypical antiepileptic levetiracetam reduces this over-activity," Gallagher said. "At the same time, it improves memory performance on a task that depends on the hippocampus." The team studied 84 subjects; 17 of them were normal healthy participants and the rest had the symptoms of pre-dementia memory loss defined as aMCI. Everyone was over 55 years old, with an average age of about 70. The subjects were given varying doses of the drug and also a placebo in a double-blind randomized trial. Researchers found low



doses both improved memory performance and normalized the over-activity detected by functional magnetic resonance imaging that measures brain activity during a memory task. The ideal dosing found in this clinical study matched earlier preclinical studies in animal models. "What we want to discover now, is whether treatment over a longer time will prevent further cognitive decline and delay or stop progression to Alzheimer's dementia," Gallagher said. Other team members from Johns Hopkins included Arnold Bakker, assistant professor of psychiatry and behavioral sciences; Marilyn S. Albert, director of the Division of Cognitive Neuroscience in the Department of Neurology; professor of neurology Gregory Krauss and the clinical study coordinator, Caroline L. Speck. Gallagher, the Krieger-Eisenhower Professor of Psychology and Neuroscience, is the founder of, and a member of the scientific board of, AgeneBio, a biotechnology company focused on developing treatments for diseases that affect brain function. The company is headquartered in Baltimore. Gallagher owns AgeneBio stock, which is subject to certain restrictions under Johns Hopkins policy. She is entitled to shares of any royalties received by the university on sales of products related to her inventorship of intellectual prop-

erty. The terms of these arrangements are managed by the university in accordance with its conflict-of-interest policies.

NeuroImage: Clinical 2015; Doi: 10.1016/j.nicl.2015.02.009

MATERIAL, CHINA

Graphene: A New Tool for Fighting Cavities and Gum Disease?

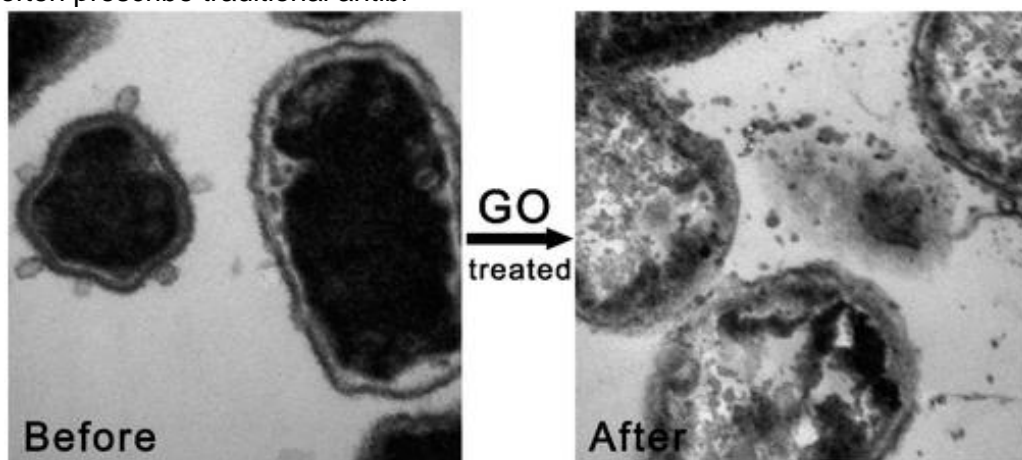
Dental diseases, which are caused by the overgrowth of certain bacteria in the mouth, are among the most common health problems in the world. Now scientists have discovered that a material called graphene oxide is effective at eliminating these bacteria, some of which have developed antibiotic resistance. They report the findings in the journal ACS Applied Materials & Interfaces. Zisheng Tang and colleagues point out that dentists often prescribe traditional antibi-

otics to get rid of bacteria that cause tooth decay or gum disease. But with the rise in antibiotic resistance, new approaches are needed to address these problems, which can lead to tooth loss. Previous studies have demonstrated that graphene oxide—carbon nanosheets studded with oxygen groups—is a promising material in biomedical applications. It can inhibit the growth of some bacterial strains with minimal harm to mammalian cells. Tang's team wanted to see if the nanosheets would also stop the specific bacteria that cause dental diseases. In the lab, the researchers tested the material against three different species of bacteria that are linked to tooth decay and gum disease. By destroying the bacterial cell walls and membranes, graphene oxide effectively slowed the growth of the pathogens. The researchers conclude that the nanosheets could have potential uses in dental care.

ACS Appl Mater Interfaces 2015; DOI: 10.1021/acsami.5b01069

CLIMATE, CHINA, USA, UK

Asian Monsoon Rains Played a Key Role in the Evolution of Mammals





New research has shown that the Asian monsoon rains played a key role in the evolution of mammals. And the findings, published today in the *Nature* journal *Scientific Reports*, could have implications for conserving the species living in the vast area affected by monsoon rains. A team including researchers from the University of Manchester, the University of Bristol, the Chinese Academy of Science, and Harvard University looked at the pattern of variation of the South Asian monsoon over time and compared it with the evolution of African mole rats and bamboo rats as revealed by a full analysis of their relationships coupled with studies of their distribution in space and through time and of their evolutionary rates. They found the first proof that weakening and strengthening monsoon rains played a key role in the evolution of these species. Over

a period of 24 million years, the changes observed in the teeth and head shape of the rodents examined, matched the varying strength of the monsoon. Of the 38 species studied only six still exist today and the changing rains seem to have driven several species into extinction. Dr Fabien Knoll, a senior researcher at The University of Manchester, said: "It was natural to assume that a mighty climatic phenomenon like the monsoon would play a part in evolution, but until now there has never been any decisive evidence thereof. We have now found that." The monsoon is a key driver of the environment in that part of the world. When it was strong forest cover and vegetation would be a lot fuller than in periods when the rains were weaker. Dr Knoll added: "We used rodents in this study because they are the most common mammals in the fossil record,

and they evolved rapidly and are very sensitive to any changes in their habitat." The researchers found that in periods when the monsoon was weaker the teeth of these rodents changed, as did other body parts they would use for digging, and they started to burrow underground. This would have provided them with resources as well as protection from predators when the forest cover was a lot thinner. The authors of this study added: "We suggest that the variations in the monsoon intensity have impacted the evolution of most, if not all, mammals living in this region, although this remains to be proved convincingly (using our methodology or others) and the pattern would probably vary from group to group."

Scientific Reports 2015; Doi: 10.1038/srep09008



**When you face the eruption
Do you feel the ending of the world?**

In China, a Church-State Showdown of Biblical Proportions

Christianity is booming in China, propelling it toward becoming the world's largest Christian nation. But as religion grows, it spurs a government crackdown.

THERE'S NOTHING secret about Chongyi Church, one of the largest in China. Its lighted steeple and giant cross penetrate the night sky of Hangzhou, the capital of coastal Zhejiang Province. Nearly everything at the church is conspicuously open: the front gate, the front door, the sanctuary, the people, the clergy. Chinese or not, you are welcome seven days a week. No layers of security guards or police exist. Walk right in. Join up. People are nice; they give you water, chat. Do you have spiritual needs? Visit their offices, 9 to 5.

For China, it is a stunning feeling. Most of the society exists behind closed doors and is tough, driven, material, hierarchical. The country values wealth, power, and secrecy – not to mention that both government and schools officially, at least, promote atheism.

Yet Chongyi looks and feels like any evangelical megachurch in Seattle or San Jose. There are big screens, speakers blaring upbeat music, coffee bars. The choir is a huge swaying wash of white and red robes. Chongyi seats 5,000 people and holds multiple services on Sunday.

“Some Sundays we are full,” says Zhou Lianmei, the pastor's wife. “We also have 1,600 volunteers.”

While Christianity is waning in many parts of the world, in China it is growing rapidly – despite state strictures. The rise in evangelical Protestantism in particular, driven both by

people's spiritual yearnings and individual human needs in a collective society, is taking place in nearly every part of the nation.

Western visitors used to seeing empty sanctuaries in the United States or Europe can be dumbfounded by the Sunday gatherings held in convention center-size buildings where people line up for blocks to get in – one service after another. In Wenzhou, not far from Hangzhou, an estimated 1.2 million Protestants now exist in a city of 9 million people alone. (It is called “China's Jerusalem.”) By one estimate, China will become the world's largest Christian nation, at its current rate of growth, by 2030.

Indeed, an acute problem facing urban churches in China is a lack of space. Chongyi Church is building a million-dollar underground parking lot to replace one that worshipers under age 30 have taken over as a meeting place.

“I come because I found a love here that isn't dependent on a person,” says Du Wang, a young businesswoman in Hangzhou. “It is like a river that doesn't go away.”

Yet there is also trouble brewing for China's faithful. As evangelical Christianity grows sharply, officials fear it could undermine their authority. Already, Christians may outnumber members of the Communist Party. That has far-reaching implications both for Chinese society and for a party that frowns on unofficial gatherings and other viewpoints. In China, party members cannot be Christian.

More than half of China's Protestants attend illegal “house churches” that meet privately. The rest go to one of China's official, registered Protestant churches, such as Chongyi. The official or legal churches, known since 1949 as the “Three-Self Patriotic Church,” operate under an arrangement that says in effect: We are patriotic, good citizens. We love China. We aren't dissidents. We go to official theology schools. So the party will let us worship freely.

And – until recently – it has.

Yet in the past year authorities have attacked and even destroyed official Protestant churches, as well as unofficial ones. Many Evangelicals feel they are now on the front lines of an invisible battle over faith in the world's most populous nation, and facing a campaign by the party-state to delegitimize them. Underneath it all is a question: Will China become a new fount of Christianity in the world, or the site of a growing clash between the party and the pulpit?

“There's an enormous struggle across China brought by the rise of worshipers that seem to really believe,” says Terence Halliday, a director of the Center for Law and Globalization in Chicago who has worked in China. “Christianity now makes up the largest single civil society grouping in China. The party sees that.”

When China opened and rejoined the world in 1979, US President Jimmy Carter asked China's Deng Xiaoping for three “favors.” Mr. Carter asked that churches shut during the

brutal Cultural Revolution be reopened. He asked that the printing of Bibles resume. And he asked that missionaries be allowed back into China. Mr. Deng accepted the first two requests, for open churches and Bibles. But he rejected the one for missionaries.

Thus began a slow restoration process harking back more than a century. The first Protestant church in China was built in 1848 in Xiamen, known then as the Port of Amoy. By the 20th century, American and British missionaries saw China as a rich field. Every city of importance had a church. Missionaries founded China's first 16 colleges, and they spurred the first reforms for female emancipation.

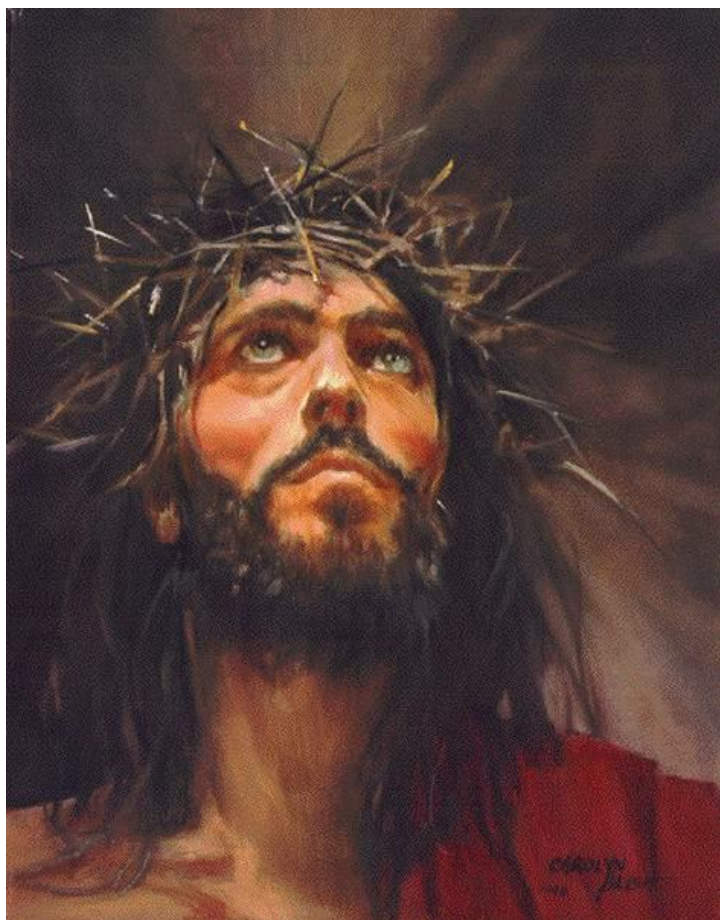
But after Mao Zedong's victory in 1949, authorities chased out the missionaries. During the Cultural Revolution from 1966 to 1972, officials closed and trashed churches as China turned violently inward. Mao partly justified the violence as necessary to bring China into the 20th century. But much of it was used to kill off his enemies, real or imagined, including the faithful.

The era produced "the most thorough destruction" of religion possibly in "human history," write scholars David Palmer and Vincent Goossaert. Authorities threw Christians in prison. They burned Bibles and executed believers to make an example.

Philip Wickeri, a leading Anglican in Hong Kong, shows visitors two Bibles that illustrate how far things went in the 1960s, and how much they have changed since. One is a small plain New Testament made of mimeographed sheets embossed with handwritten Chinese characters. It is a Cultural Revolution-era "samizdat" Bible, painstakingly produced. Different church cells memorized single books

of the New Testament, copied them, and then combined them to form a single gospel. The shadowy venture lasted several years, during which 150 Bibles were made.

Mr. Wickeri's second Bible is



gilt-edged and nestled in a rich box of bamboo. It is dated 2012 and was produced by the Amity Printing Company in Nanjing. It was part of a run that included the 100 millionth Bible published in China since the opening in the early 1980s.

For decades, Christianity here was considered something for older female peasants. But the demographics of religion are changing dramatically. China's new faithful are younger, more educated, more urban, and more affluent.

One surprising change is that a majority of believers no longer view Christianity as something foreign. They increasingly view faith as transcending its Western missionary-derived system. Many Chinese no longer accept the idea that being

Christian means forfeiting a Chinese identity.

Last summer, China's religious affairs chief said that 500,000 Christians are baptized each year in the country. A joint study between Baylor University in Waco, Texas, and Peking University in Beijing estimated that there are now 70 million Christians over age 16 in China. Communist Party membership is about 83 million.

Even so, no precise numbers exist for the total number of worshipers. Chinese government statistics put the rise in Protestants in the official churches at 800,000 in 1979, 3 million in 1982, 10 million in 1995, and 15 million in 1999. There the accounting stops. Carsten Vala, an expert on religion in China at Loyola University Maryland in Baltimore, says 40 million to 60 million is "the low end of a conservative" estimate of the number of Evangelicals. Fenggang Yang, director of the Center on Religion and Chinese Society at Purdue University in Indiana, says he thinks there are more than 80 million Christians and that China will have 245 million by 2030 if growth is steady – making it the world's most populous Protestant nation.

In some ways this surge seems counterintuitive. Being a Christian in a country that sees worship as odd or superstitious does nothing to boost one's status. "There is absolutely no social advantage to being a Christian in China," says Bob Fu, a pastor who escaped a Chinese police crackdown in the 1990s and now runs Texas-based ChinaAid, which monitors Christian rights in the country. "There are no cookies, no status, no outward rewards, no privileges in choosing Christianity."

Yet as Chinese achieve material wealth and success, many feel lost. The success of economic reforms un-

der Chinese leader Deng, launched in the early 1990s, has not helped rebuild China's spiritual infrastructure, decimated during war and the Cultural Revolution. China's rise has come with a cost: a loss of traditional values and the rise of cheating, corruption, and fierce competition. As Orville Schell, the Arthur Ross Director of the Center on US-China Relations at the Asia Society in New York, points out, there are 150 billionaires in China but little certainty.

"Everyone is groping and grasping," he says. "People are turning to Buddhism, Christianity, self-help, and Taoism. CEOs and billionaires run around with their spiritual masters and visit meditation rooms."

In dozens of interviews with believers in official and house churches, the word they use most for why they turn to church is "love." "Chinese have a yearning heart, that is really the reason," says one woman who goes to the Zion house church in Beijing, which has more than 10,000 attendees and whose pastor is Korean. "We need love, and in some ways it is that simple."

One Chinese intellectual and former newspaper editor agrees that China has become sated and corrupt. But he doesn't agree there is a significant turn toward spiritual matters.

"We are too comfortable and willing ... to say 'yes' to anything," says Li Datong. "I wish there was more spiritual hunger."

Yet Chinese parents complain of a society that teaches math and science in schools but does little to address conduct or character. The case of Little Yueyue is a symbol of the moral void. The 2-year-old girl was hit by a van in Guangdong a few years ago. The driver didn't stop. The girl was thrown to the side of the road, and 17 people walked past before an itinerant migrant stopped to help. The event was captured on a video that went viral and spurred some national soul-searching.

Experts say the Chinese have a practical nature, and if they adopt the evangelical message, especially after

years of required wrestling with Marxist thinking, they usually don't take it lightly. Many work hard at it.

"Chinese Christians know the Bible better than some Southern Baptists," says Wickeri in Hong Kong. "That's not a small thing."

Typical is the pastor Han Yufang at Chongwenmen Church in Beijing. Ms. Han is one of many women now being ordained in official churches. But for years her father forbade her to look into Christianity. She did anyway, studying it for seven years, the final two praying for most of each night. One evening she was on her knees by the bed and prayed to God, "Father, not my will but thine be done." She says she felt a clear urge to study at a divinity school.

Another woman, a mother in her 40s, first went to church with friends. She says she felt nothing but kept going to be part of the group. She dabbled. She tried Buddhism, but, "for all the quiet, I never really found peace." During one service the concept of "forgiveness came from nowhere and washed and melted me in a way I can't describe," she says. At the time she was "always fighting" with her husband. After the experience, the tension stopped. He also started attending church services with her, as did their son, who finds Bible stories "compelling."

For the most part, Protestants try to keep the altruistic activities they do in society quiet and low-key. China officially recognizes five faiths – Islam, Catholicism, Protestantism, Buddhism, and Taoism. But only Buddhism and Protestantism are experiencing lively growth. Evangelicals do not want to draw attention to themselves and perform most of their good works without publicity.

Yet in cases such as the Sichuan earthquake in 2008, which killed 70,000 people, churches sent groups to help on the ground. By some estimates, as many as half the volunteers were evangelical.

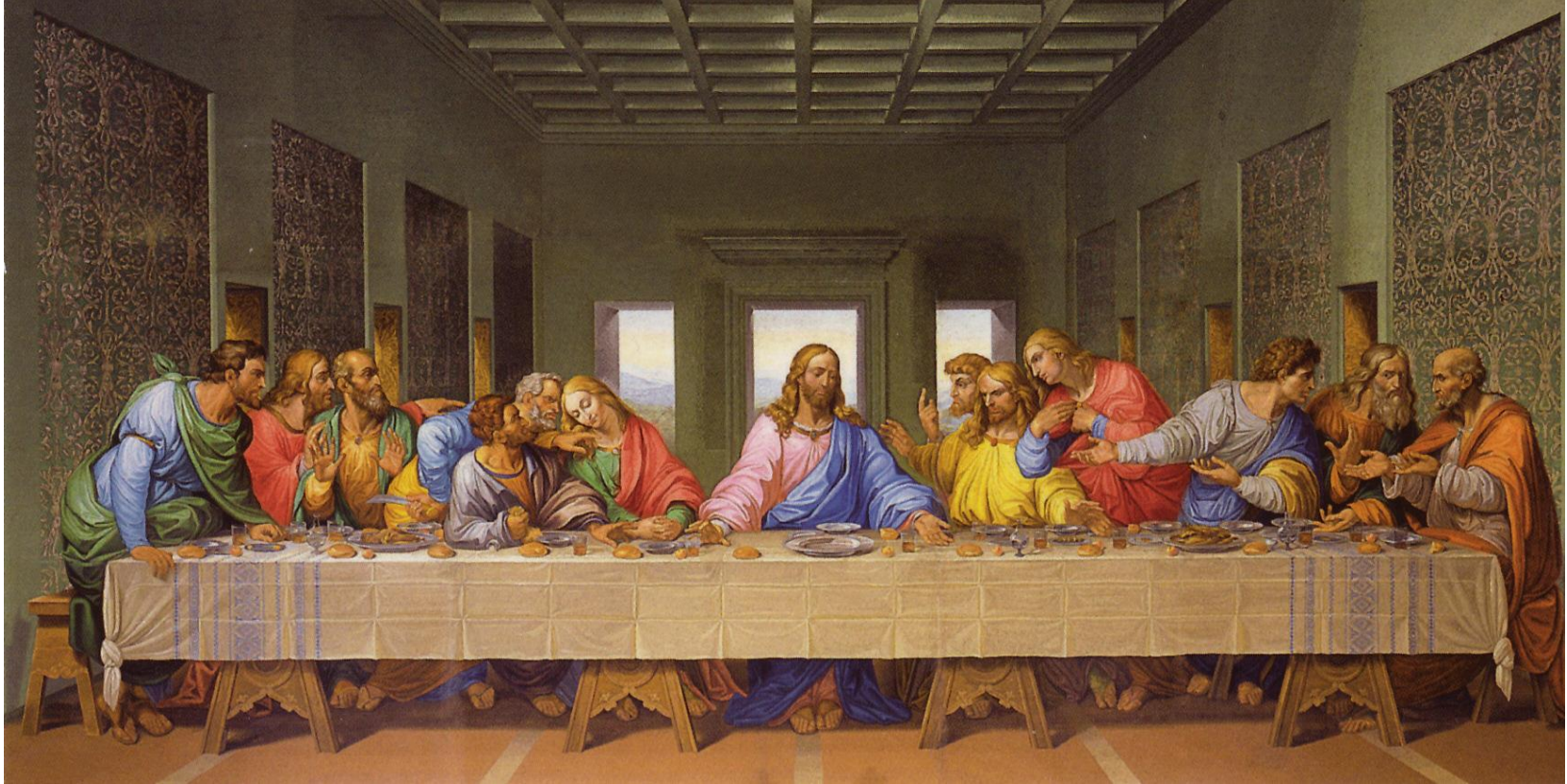
Some Christians are trying to improve business practices and fight corruption as well. One business group

asks members to pledge a "Ten Commandments" of good behavior that includes no bribing, no taking mistresses, no avoiding taxes, and no mistreating employees. Zhao Xiao, a researcher at the University of Science and Technology in Beijing, tells of a Christian in Harbin who lost \$8 million his first year applying the principles but is now a leader in his industry.

One January morning last year in Hangzhou, Chinese officials showed up unexpectedly at the Gulou Church. It is a massive gray-stone edifice across the famed West Lake from the Chongyi Church. The Gulou clergy was informed that the cross on their edifice was scheduled to come down. Church leaders were stunned. It was the first they'd heard of any plan to remove the cross. Then for much of the spring, they and other Christians in China heard of little else, as both official and unofficial churches were raided, destroyed, or dismantled in a campaign that has lasted more than a year.

Gulou itself was established by Presbyterian missionaries in the 1880s. The cross atop the steeple was enormous, a fixture next to a well-known highway overpass. It is dear to members as a symbol of their faith, says a pastor who declined to be named. For months, Gulou's leaders delayed the removal of the cross. Meanwhile, authorities attacked churches and, as of this writing, have stripped or desecrated more than 426 of them, including knocking one down while President Obama was visiting Beijing last fall. In many cases, tearful worshipers surrounded the churches and scuffled with police. Zhejiang itself has become ground zero in China's growing clash between church and state.

On Aug. 7 at 5 p.m., authorities returned to Gulou. They summoned the head pastor and said that at 10 p.m. the cross would be removed by crane. Word got out (the pastor only told one person since he could otherwise be jailed for calling an unofficial gathering). The church was surrounded by worshipers praying and chanting "cross, cross, cross."



“We felt helpless,” a junior pastor says. “We told them how important this cross is, but they didn’t listen.”

“They can take the cross from our church,” he adds, “but they can’t take it from our hearts.”

Crackdowns on Christians are nothing new in China. What is different is how broad and systematic the suppression has been and how the state, for the first time, is attacking official churches. To be sure, it was clear by summer that Chinese President Xi Jinping was conducting a harsh roll-up of civil society in general – artists, lawyers, scholars, as well as Christians – as part of a new emphasis on orthodox party thinking and rules.

“The party isn’t satisfied with just keeping people behind a great firewall,” says one lawyer. “They actually want to indoctrinate.”

So far, the cross on Chongyi Church remains intact. But Evangelicals here who thought they were adhering to the proper political decorum are not happy. “People are angry and feeling betrayed,” says a local volunteer who did not want to be named for fear of retribution. “If I were the government I would not do this.”

Why authorities would alienate believers who think of themselves as loyal Chinese is unclear. Many local Christians first thought it was a mis-

take or something engineered by local authorities in Zhejiang Province. Officials said large crosses near highways were a driving hazard.

But as more churches lost their crosses, many far from highways, and other official churches were bulldozed, feelings changed. One church quietly offered to pay a series of fines, thinking the attacks were about money. “We were fooled at first,” says one local pastor. “Then we discovered they didn’t care about fines. They went after our crosses and gave the impression they enjoyed it.” The aim was to humiliate and shame, he says.

In recent years, Evangelicals in east China were “doing well,” the pastor continues. “But that is now changing. We are going backwards now. Everything is changing with the new leadership in Beijing. We know what is happening. We are not visitors here.”

Zan Aizong, a local journalist who became an Evangelical, says the government is trying to clamp down on churches and faith without causing a global outcry. Officials “use the legal system,” he says. “They go after crosses and building codes because it will not cause an uproar abroad. They want to turn Christianity into Chinese Christianity, controlled by the party.”

In August, amid the suppression in Zhejiang, the party issued a state-

ment that it would soon unveil an official Christian theology. Wang Zuoran, head of China’s religious affairs ministry, told the state-run Xinhua news agency that Christianity was spreading so rapidly that a new theology was needed to avoid problems. “The construction of Chinese Christian theology should adapt to China’s national condition and integrate with Chinese culture,” he said.

As the attacks continue, church leaders are debating how to respond – whether to publicly challenge the crackdown or try to ride it out, the argument being that authorities could do much worse things if provoked.

“Many Christians are scared of the government,” says Ling Cangzhou, a Christian blogger in Beijing. “In China you rely on the government for jobs, position, for money. Families and relatives are affected. Dissidents don’t get promotion or advancement.”

One effect of the new religious persecution in China is that it is bringing the official and unofficial wings of the Protestant Church closer. For years, the two sides have often been clashing siblings: In essence, private house churchgoers saw the Three-Self churches as compromised by the party. Official churches often saw house churches as misbehaving cults.

Yet now, as they share a common threat and as more young people take up Christianity who has little knowledge of the historical divide, the two wings are starting to converge, reinforcing a grass-roots movement that has already been under way for some time.

Worshippers are being introduced to Christianity in official churches and then moving to house churches for a deeper experience of Bible study and preaching. In turn, house churches are becoming less secretive and are reaching out to influence the official churches. “There is a growing but quiet cooperation among Three-Self pastors who aren’t as invested in the institution – who care more about church and the basic evangelical mission,” Mr. Vala says.

To be sure, real differences remain between the two sides. Three-Self pastors are trained at theology schools watched by the party. Mr. Zan, for example, attended one and says

that former President Hu Jintao’s concept of a “harmonious society” was taught as something to emphasize in preaching, which Zan calls “propaganda.” “Official churches are not allowed to touch subjects like the Apocalypse or eschatology,” he says. “A lot of the preaching is about how to be good and loving and ethical, which is fine. But they are often antiseptic and less radical.”

Many house meetings last all day, whereas official churches have 60- to 90-minute services. “The [Three-Selfs] are too big,” says a musician from Anhui who started at an official church but moved on. “You can get lost in them. Smaller is more like home, more like the love you feel at home.”

In Beijing, the official Chongwenmen Church is near the train station, found by walking through a rabbit warren of streets and noodle shops. It is old and slightly creaky. Services are packed and believers are devout.

Across town, the official Haidian Church is a huge white modernist structure in a high-tech zone. Outside there is a band and chorus and kids with “I [heart] Jesus” caps. People wait in line for services by the hundreds.

One private Calvary church feels much different. Set in a seminar room in an office tower, it seems far less institutional but more intimate. The pastor is from Taiwan and won’t talk with reporters. Yet in all three churches the focus is on Christianity as a life practice and not a philosophy, and of the Bible as a revelation whose meaning brings change and redemption.

During services at these churches in August, as the cross removal campaign intensified, pastors spoke openly of the “meaning of the cross.” Hymns sung included “‘Onward, Christian Soldiers’ ... with the cross of Jesus, going on before.” ■



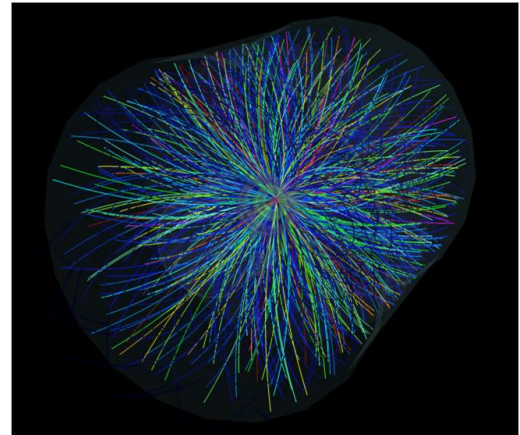
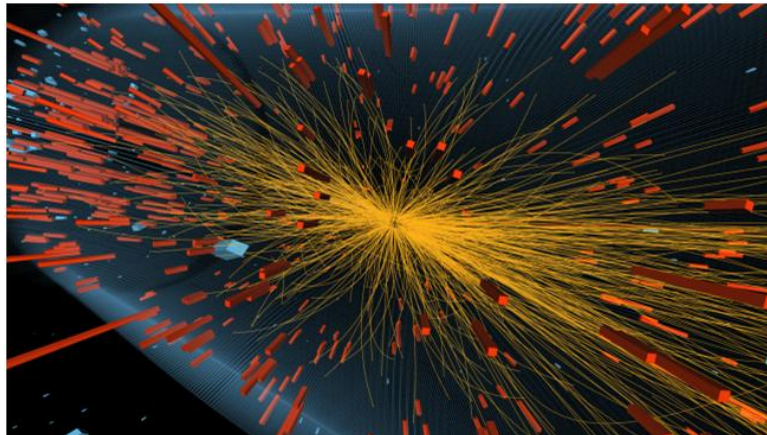
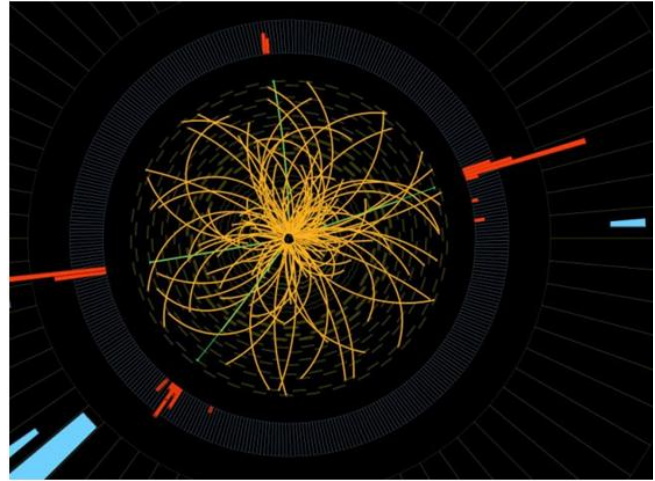
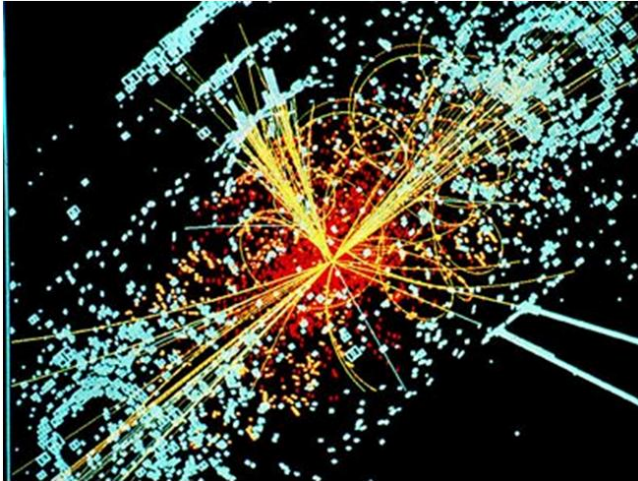
Working like a worker bee?
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What Will Happen When Two Proton Beams Collide at Nearly the Speed of Light?

By Kelly Dickerson (2015, USA)

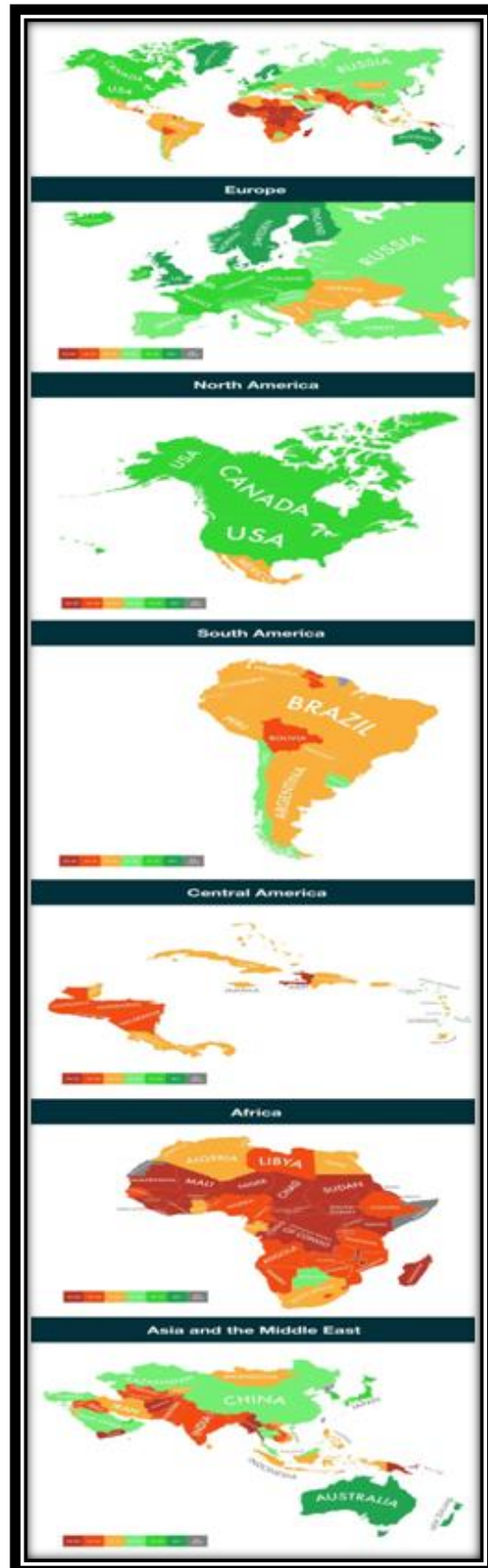


When protons barrel into each other in head-on collisions, they explode into hot clouds full of exotic subatomic particles: The first step is to turn hydrogen into protons. Hydrogen is a special element because its atoms only contain two particles: an electron and a proton. Other elements have atoms with multiples of each and also have neutral particles called neutrons. So it's simpler to isolate protons this way: Just use an electric field to pull electrons off hydrogen atoms, leaving lone protons. A beam of isolated protons is then sent speeding clockwise around the giant 17-mile-long tunnel of the LHC, while a second beam of protons is sent counterclockwise. The LHC has a series of accelerator tubes that rev up the proton beams' speed until they're traveling just a fraction of a second under the speed of light. Supercooled magnets line the tunnel and act like a steering wheel to keep the beams on track. Each proton beam holds 2,000 to 3,000 bunches of protons, and just one bunch is made of about 100 billion protons. Before the beams collide, all those protons are squeezed into a stream that's less than the width of a hair. The LHC will create roughly 600 million collisions per second when it revs up to full power a few months from now. The collisions happen at four points along the 17-mile-long ring. A particle detector is waiting at each point to measure all the subatomic particles that erupt from the collisions. Scientists think this second run of the LHC will reveal a whole suite of new particles that could completely change what we know about physics. The tunnels of the LHC that the protons flow through have vacuum-like conditions similar to that of empty outer space. When two beams collide, all that energy packed into such a small vacuum of space explodes and creates mass in the form of subatomic particles (think of Einstein's famous equation: energy equals mass multiplied by the speed of light squared). The particles that spawn from these collisions only exist for a fraction of a second, but that's enough time for the particle detectors to do their jobs — to measure the position, speed, charge, mass, and energy of all the subatomic particles that are created. The original article was from the [BUSINESSINSIDER](#).

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Epigenetic Modification of Nociceptive Mediators: Implications for the Etiology of Neural Hypersensitivity (Part I)

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SUMMARY Many factors have been identified contributing to the pathogenesis of pain, whereas we still cannot conquer the pain based on these findings suggesting that further studies are needed and other more potent mediators should be investigated. Epigenetics, in contrast to genetics, refers to the functionally relevant modifications to the genome that do not cause changes in underlying DNA sequence. These kinds of changes in gene expression or cellular phenotype regarded as landmarks of epigenetics are regulated by different types of modifications including gene methylation, histone acetylation, phosphorylation, imprinting and reprogramming etc. We, in this part (Part I), will review the general epigenetic modifications on molecular mediators on biological processes as the preface of the second part of the whole article (Part II will be available in the June issue of the journal). This general understanding of the epigenetic modification on the modulating factors that influence individual differences from pain sensitivity and responsiveness to analgesics possesses crucial clinical implications. ■

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OVER HUNDREDS of molecules so far were identified being involved in the regulation of the pathogenesis of pain, and they were classified into four categories: neurotransmitters (amino acids, monoamines, peptides and gaseous transmitters), cytokines (pro- and anti-inflammatory), endocrine and immune-mediators (hormones and human leukocyte antigen system), and second messengers and nuclear mediators (calcium, cAMP, NF-κB, menin etc.). Rare clinic-suitable drugs were

found to control over the pain when different pharmacological activators or inhibitors were administered through focusing on these various kinds of molecules (1, 2). Consequently, studies began to concentrate on the genetic control on pain and increasing evidence appeared showing that genes are the primary signature of pain with individual difference and also the determinant of the development of chronic pain (3). Nevertheless, we cannot change the gene sequence that has mutated before the pain appearance, and also we do not know what will be happened next to the already-happened pain because it is really difficult to predict the genetic changes under the present knowledge of science. Unlike genetics, epigenetics is the study of changes in gene expression and cellular phenotype otherwise the underlying DNA sequence (4). The development of epigenetics promises patients hope for controlling the pain through modifying the gene expression of pain-related molecules that finally determines the fate of the patient's outcome.

Nociceptive Transduction and Mechanisms

Before the central nervous system (CNS) feels pain, the injury first needs to be sensed by nociceptors located at the terminals of the peripheral nerve fibers through forming action potentials (APs), and then these APs will be transmitted into the first delay station – dorsal root ganglia (DRG) followed by complicated modulation at the dorsal horn of the spinal cord. After modeling by the dorsal cell groups, the signal will be transduced upward into specific areas of the brain where the pain signals are remodeled and perceived. This is the so-called ascending facilitation. However, it is not ended after the pain was felt. The CNS activates its self-control mechanisms, i.e. the descending inhibition, through which the original pain signal was diminished. This is the macro-description of the pain transduction, but a more complex neural network is

formed underlying this “ascending-descending” balance.

Facilitation of Nociception

Excitatory neurotransmitters are considered as the major compositions of the ascending facilitation-associated molecules for pain transduction. Glutamate, the principal excitatory neurotransmitter in the CNS, takes role by binding two types of receptors: ionotropic and metabotropic receptors (5). The ionotropic receptors include N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (KAR), which are ion channels; and the metabotropic receptors belong to G-protein coupled receptors named mGluRs. Abundant evidence showed that NMDARs are critically involved in synaptic plasticity and pain facilitation in the CNS that has long been considered a target of pain management (6), and the AMPAR subunit trafficking in the dorsal horn contributes to the hypersensitivity that underlies persistent pain (7), and KAR plays integral signaling role at multiple levels of the pain neuraxis (8). Focusing on these types of receptors potentiates novel therapeutics via inhibiting their activities with pharmacologically or genetically developed probes. To the mGluRs, the final effect of their activation depends on their anatomic location and the signaling cascades to which they couple, from which both of the pro- and anti-nociceptive effects can be developed (9). Although increasing reports presented evidence supporting glutamate's involvement in the regulation of the pathogenesis of different types of pain, we still cannot find ideal interventional means targeting on its multi-functional receptors. Furthermore, the precise relationship between glutamate and descending inhibition is still unknown.

Pro-inflammatory cytokines are another major kind of contributors to the ascending facilitation of pain (10). The localized inflammatory “soup” either at peripheral injury site or at the

CNS facilitates sub-threshold stimuli to APs leading to hyperalgesia (11). Over a hundred of cytokines were identified and evaluated for their involvement in the modulation of pain. Tumor necrosis factor- α (TNF- α) is one of the key contributing factors to pain (12), and Etanercept, the monoclonal antibody of TNF- α , is the first drug available in clinics for controlling inflammatory responses from which the pain was alleviated (13). Interleukin-1 β (IL-1 β) is an essential cytokine with broad-spectrum expression property (from peripheral to central) in the context of pain (14), and blockade of IL-1 β is a potential target of pain therapy. Macrophage migration inhibitory factor (MIF), the earliest-discovered cytokine named on its inhibitory effect on T-lymphocyte's random migration, has been identified as a pro-inflammatory cytokine contributing to the pathogenesis of pain by activating corresponding receptor CD74 (15), and the inhibitor focusing on its tautomerase activity was a promise means in controlling pain (16). Cyclo-oxygenase (COX) is a kind of enzyme responsible for the formation of prostanoids, an important mediator of inflammation (17), and pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain (18). The expression of all these mentioned molecules after pain displayed different levels of upregulation, and blockade of them is considered a critical means of analgesia. Whether these inhibitions can produce as expected effect or not still needs to be investigated further.

Ion channels are a group of pore-forming membrane proteins functioning establishing resting membrane potential and shaping APs through gating the flow of ions across the cell membrane. Sodium channel, one of the major basal channels forming APs, was extensively studied especially the voltage-gated sodium channel on its role in pain and found that the creation of aberrant sodium channel clusters served as sites of ectopic sensitivity or spontaneous activity that is strongly associated with the development of

pain (19). Potassium channel, the most diverse class of ion channels, exerts function through shaping APs and setting the resting membrane potential. Although a complex distribution of the voltage-gated potassium channels among sensory neurons exists, the physiological importance of potassium channels in nociceptive neurons was well documented (20). Voltage-gated calcium channels have been recognized as potential targets for analgesic development, but the availability of the related analgesics is rare (21). Chloride channel, a poorly understood ion channel, has also been found being involved in the mediation of nociceptive transmission (22). In most studies, chloride channels were activated indirectly as the sequence of other ion channels' activation (23, 24), and also the calcium-activated chloride channels are involved in the delta-opioid receptor-mediated central antinociception (25). What is the precise interrelationship among these ion channels and their contributions to facilitating pain are still not elusive and further studies are needed on this topic.

Inhibition of Nociception

Opium, the first opioid discovered for pain relief, is the most widely-used medicine around the world and its history can be traced back to the Neolithic Age (26). Until 1804, morphine was first isolated by Dr. Friedrich Sertürner and it then became the most abundant opiate (27). Till today, morphine is still the most widely used analgesic by clinicians, whereas overwhelming evidence also criticized its side effects and the potential addiction. Even different types of opioids were synthesized, but the tolerance to opioid analgesics reduced the expectation of this kind of drug and promotes researchers to find suitable alternatives; in contrast to the tolerance, opioid-induced hyperalgesia is another challenge for health care-givers (28, 29). Beside exogenous opioids, the endogenous opioidergic system is a crucial part of the descending inhibition,

which includes endorphins, enkephalins, dynorphins and endo-morphins (30). The activation of different types of receptors (mu, MOP; delta, DOP; kappa, KOP and nociceptin, NOP) is the basis of opioid analgesia. During chronic pain conditions, the endogenous opioidergic system encountered significant changes leading to overbalance of the self-adjusting ability, after then the pain was worsened (31). Therefore, we can conclude that the opioidergic system has dual effect, i.e. pro- and anti-nociception, and the final effect is based on the balance between these two facets. Additionally, evidence appeared showing that the opioidergic system is combined with other systems like the adrenergic (32) and the GABAergic (33) suggesting that in-depth experiments are necessary to clarify their precise relationship.

Gamma-aminobutyric acid (GABA), the key inhibitory neurotransmitters in the CNS, is a major component of inhibitory neuroactivities including descending inhibition. Experimental evidence showed that impaired GABAergic transmission was an important cause resulting in pain (34). The death of GABA-containing interneurons after nerve injury and altered storage or/and release of GABA are possible underlying mechanisms of the loss of GABAergic inhibition (35). Both types of GABA receptors (types A and B) all are involved in the process of pain-related central sensitization (33, 35). How to reach the ideal level of GABA and how to keep the GABA receptors at the optimum function are two problems that need to be solved when GABAergic system was considered as the target of pain management.

Monoamine neurotransmitters including noradrenalin, serotonin and dopamine form a complex interaction each other to exert inhibitory function on pain (36). Intrathecal clonidine, a centrally acting α_2 adrenergic agonist, produced dose-dependent analgesia (37) suggesting that spinal adrenergic system is involved in the process of pain-coding. More recent clinical evi-

dence showed that intrathecal (38), topical (39) and intravenous (40) administration of clonidine produced effective analgesia. Given the strong association among the three monoamines, the currently available drugs – antidepressants which have combined effect on two or three of them have been studied at length and now they are approved for the use in pain control (36). Furthermore, different types of subunits of the monoamines' receptors determine the complex final effect if one drug has mixed role in activating or deactivating two or more subtypes of these receptors, and undoubtedly the side effects would be consequently resulted from (41). As thus how can we realize our pain-relief purpose through fine-tuning the monoaminergic systems? It is herein hard to reach this goal.

Anti-inflammatory cytokines, in contrast to the pro-inflammatory cytokines, were regarded theoretically as one part of the descending inhibition (10, 42). Although we describe the pro- and anti-inflammatory cytokines separately as ascending facilitation and descending inhibition, respectively, they actually exert functions simultaneously when the injury occurred peripherally or centrally. IL-10 is the major anti-inflammatory cytokine found to be involved in the modulation of pain and hematopoietic stem cell transplantation was considered a potential method to treat IL-10 and IL-10 receptor deficiency (43). The transforming growth factor- β (TGF- β) superfamily is a multifunctional, contextually acting family of cytokines, and found TGF- β was a relevant mediator of nociception and has protective effects against the development of chronic pain by inhibiting the neuroimmune responses of neurons and glia and promoting the activation of the endogenous opioidergic system in the CNS (44). Interferon-gamma (IFN- γ), an essential macrophage-activating factor, was found to be an important regulator of pain even though most studies on this cytokine were focused on its immunostimulatory and immunomodulatory effects (45).

So it is still necessary to find easy-to-use methods to relieve pain by concentrating on above-mentioned molecules through modifying their corresponding genes, a prospectively promise for conquering pain, especially for the refractory chronic pain.

General Epigenetic Modifications

The word “epigenetics” was coined by Dr. Waddington, C.H. in 1942 as a portmanteau of the words *epigenesis* and *genetics* (46), and its original meaning was the heritable changes in gene function that were not explainable by changes in the DNA sequence. The more precise definition of epigenetics is largely based on the recent understanding on its underlying mechanisms as it is the structural adaption of chromosomal regions in order to register, signal or perpetuate altered bioactivity states (47). As the basic thought considered that why the same gene yet performs distinct functions, the answer is that it is the epigenetic achieve the goal by switching on and switching off specific gene expression. The major reason for epigenetics became popular and be a hot topic for research is that it is reversible and therefore have the potential to be manipulated therapeutically (48). Epigenetic control on gene expression is reached by methylating DNA or/and histone or/and acetylating histone, and these processes take place generally in combination each other.

DNA Methylation

DNA methylation, unlike the histone modification, occurs with limited variability through adding a methyl group to the 5 position of the cytosine pyrimidine ring or the number 6 nitrogen of the adenine purine ring (49). As the biochemical process of gene expression forwarded, a number of molecules function as the writers (attachment) or erasers (removement) or readers (binding) of the modifications to DNA to a specifically epigenetical-

ly modified site, and then take role in the regulation of gene expression (50). As the first studied epigenetic type, DNA methylation can stably change the expression of genes, and permanently and unidirectionally transduced. CpG islands are the genomic regions containing a high frequency of CpG sites where they are enriched in promoters in vicinity to transcriptional start sites and the methylation on them has been associated with long-term gene silencing including X-chromosome inactivation (49). DNA methylation typically occurs in a CpG dinucleotide context, but non-CpG methylation is prevalent in embryonic stem cells. In general, DNA methylation occurs mainly at the C5 position of CpG di-nucleotides and is carried out by two general classes of enzymatic activities – maintenance methylation and *de novo* methylation (51, 52). Maintenance methylation is a necessary requirement to keep the gene being methylated after every cellular DNA replication cycle, and *de novo* methylation is the subsequent alterations to the changes of environments and is more flexible the maintenance methylation. DNA methyltransferases (DNMTs) are enzymes regulating the methylation of DNA, and they are composed of three subtypes: DNMT1, DNMT3a and DNMT3b (53). It is thought that both DNMT3a and DNMT3b are the *de novo* methyltransferases functioning to set up DNA methylation patterns early in development, but DNMT1 works to maintain the methylation in the semi-conservative way. However, these three types of DNMTs appear to maintain and reestablish the methylation patterns (54).

Histone Methylation

Histones, the chief protein components of chromatin, are located in eukaryotic cell nuclei to structure the DNA into nucleosomes. Histones are classified into five major families: H1, H2 (subtype A and B), H3, H4 and H5. H2A, H2B, H3 and H4 are considered as the core histones, but H1 and H5

are regarded as the linker histones (55). The methyl groups are transferred to amino acids of histone proteins of chromosomes is named histone methylation, which mainly occurs at lysine and arginine residues of histones H3 and H4 which can be mono-, di- and tri-methylated (56). Methylation and demethylation of histones, in most cases, switch the specific genes “off” and “on”, respectively. Histone methylation occurs by loosening but demethylation by encompassing the tails which results in respective permission and blockade of the transcription factors to access the DNA (57). Lysine can be mono-, di-, or tri-methylated, but arginine can only be mono- or di-methylated. Different degrees of residue methylation generally resulted in different functions (56). Histone methylation needs the involvement of the histone methyltransferases via transferring the methyl group from S-Adenosyl methionine onto the lysine or arginine of the H3 and H4 histones. In addition, there are proteins possess histone demethylase activities like the lysine-specific demethylase family and the Jumonji C family (58, 59). The balance between histone methylation and demethylation requires accurate interaction between histone methyltransferases and demethylases.

Histone Acetylation

Histone acetylation leads to activation of transcriptional activity by decondensating the chromatin, but histone deacetylation on the contrary reduces transcriptional activity by condensating the chromatin (60). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are the major enzymes catalyzing above two activities. In consideration of the role of these two enzymes through neutralizing and restoring the positive charges in lysine residues, they are regarded as transcriptional activators and repressors, respectively (61). Based on these, HATs and HDACs became the focuses of studies using different types of pharmaceutical interventions.

HATs are classified into two different categories on their subcellular location: type A localized in the nucleus and type B localized in cytoplasm. Type A HATs are responsible for the regulation of gene expression by acetylating nucleosomal histones, but type B HATs are involved in the process of acetylating the newly synthesized histones before they assembled into nucleosomes (60, 62). To HDACs, four different classes exist: class I (HDAC 1-3 and 8), class II (HDAC 4-6, 7-10), class III (sirtuin, SIRT 1-7) and Class IV (HDAC 11) (63). Classes I and II are the typical HDACs whose activities can be inhibited by trichostatin A (TSA), class III belongs to the family of nicotinamide adenine dinucleotide-dependent proteins not affected by TSA, and class IV is an atypical category. HDAC inhibitors have long been used to treat epilepsy and to stabilize mood (e.g. valproic acid), and the recently approved vorinostat (SAHA) and romidepsin (FK228) for cutaneous T cell lymphoma (64).

Other Epigenetic Modifications

In except of above-mentioned three major epigenetic modifications, histone ubiquitination and sumoylation are two other epigenetic means largely producing covalent modification of histones (65, 66), and histone phosphorylation stimulates histone acetyltransferases to promote histone acetylation and subsequently enhance transcription (67). Ubiquitination is considered as a signaling module from which the signal transmitted mainly on the nature of the modification, such as mono- or poly-ubiquitin or the lysine residues onto which the ubiquitin binds (68). Even the ubiquitinated H2A and H2B so far have been reported, but their precise roles are still not elucidated. Histone sumoylation regulated gene silencing by recruiting histone deacetylase and heterochromatin protein 1 (69). Besides, histone ADP-ribosylation, another epigenetic modification, facilitates gene transcription by directly remodeling nu-

cleosomes (70). Although these different types of epigenetic modifications exist to control and mediate the chromatin remodeling processes sophisticatedly, it is really difficult to figure out the intricate crosstalk that occurs amongst them each other.

In sum, from peripheral to central sensitization, from ascending facilitation to descending inhibition, from neurotransmitters to cytokines, from DNA to histone modification to protein expression, all have great potential of finding novel therapeutic targets for the treatment of pain. The combined investigation between pain research and other disciplines like computational science and bioinformatics would provide in-depth insights in clarifying their interactions and finding potential more specific therapeutics. ■

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Eight Foods That Help Improve Your Memory

By Lisa Freedman (USA)

FORGOT what you're looking for? Bad with names? Writing down a lot of lists but then misplacing them? Like most people, you're experiencing some memory loss—and growing older doesn't help matters. Luckily, researchers all over the world are scouring the earth looking for ingredients that might organically improve human recall. Scan the menu of ingredients below and, if you make the right diet changes, you too could develop a champion's memory.

Salmon

There's a reason that fish is called brain food, says Lauri Wright, PhD, RD, LD, and assistant professor of nutrition at the University of South Florida and a spokesperson for the Academy of Nutrition and Dietetics. "Several studies have shown that a diet containing generous amounts of omega-3 fatty acids leads to decreased rates of dementia and improved memory recall," she says. Researchers at the Rush University Medical Center in Chicago followed more than 6,000 people for four years to see how diet affected their memory. The frequent fish eaters (at least once a week) had a 12 percent slower memory decline than those who did not eat fish. The fish eaters also saw a 60 percent reduction in the risk of developing Alzheimer's disease. Wright suggests three four-ounce servings each week of omega-3-rich fatty fish like salmon, mackerel, herring, and sardines.



Curry

Plan a weekly Indian takeout night: Researchers have found that curcumin, a primary ingredient in turmeric and curry powders, slows the formation of plaque deposits and even destroys accumulations in mouse brains. These plaque deposits—known as amyloid plaques—have been linked to the development of Alzheimers. Curry has also been proven to help prevent cancer and heart disease.



Blueberries and Grapes

"Berry fruits and vegetables contain compounds that are important for optimal function and resisting decline with aging," says Robert Krikorian, PhD, who leads the Cognitive Aging Program at the College of Medicine at University of Cincinnati. One of his studies found that those who drank blueberry juice every day for two months significantly improved their performance in learning and memory tests. In another study, he found similar results with Concord grape juice.



Beets

Not only are beets super trendy these days, they're also loaded with nitrates. Great—but what are nitrates? "Nitrates are a form of nitric oxide,



which is a natural compound that is involved in vascular dilation (and associated blood pressure lowering),” explains Krikorian. So the nitrates increase blood flow and oxygen to the brain, thus improving mental performance.

Spinach and Kale

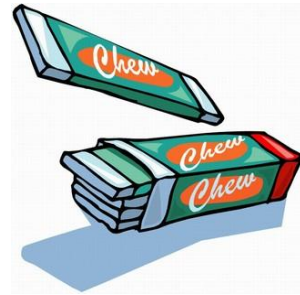


Leafy greens contain antioxidants and they're also loaded with a significant amount of folate. “Studies have shown that folate-rich foods improve memory by decreasing inflammation and improving blood flow to the brain,” says Wright. Folic acid has also been proven to lower levels of homocysteine, an amino acid linked to a higher risk of heart disease. In a study published in the *American Society for Clinical Nutrition*, researchers followed 321 men for three years and tracked their levels of homocysteine; those with

higher levels showed memory decline and those who ate foods rich in folic acid seemed to fight memory decline.

Chewing Gum

If you're on deadline at work, try popping a piece of Trident into your mouth. During a 2013 study, researchers at Cardiff University had two groups of people each listen to a 30-minute recording of a sequence of numbers. When asked to recall the sequence later, the group that chewed gum had higher accuracy rates and faster reaction times than the group without the gum. “This suggests that chewing gum helps us focus on tasks that require continuous monitoring over a longer amount of time,” the lead author of the study, Kate Morgan, explained.



Coffee

Can't remember where you put your phone? (Oh, that's right, it's in your hand ...) Have a cup—or three—of Joe. Researchers from the University of Innsbruck in Austria found that the caffeine equivalent of about two cups of coffee increased brain activity in two locations, one of which is involved with memory. And a study by researchers at the French National Institute for Health and Medical Research found that women over 65 who drank three or more cups of coffee a day were better at recalling words than women who consumed little or no coffee.



Chocolate

You can swap in a cup of hot chocolate for coffee if you prefer: A 2013 study found that older adults (73 years old, on average) who drank two cups of cocoa every day for a month had improved blood flow to the brain and performed better on memory tests. Or try a bar of dark chocolate (with at least 70 percent cocoa), which is a good source of flavonoids, antioxidants that have been linked to brain health. The original article was from [YAHOO](#).



FREEDOM



RIOT

TODAY'S WORLD

who should pay for this...



AUTHOR GUIDE

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