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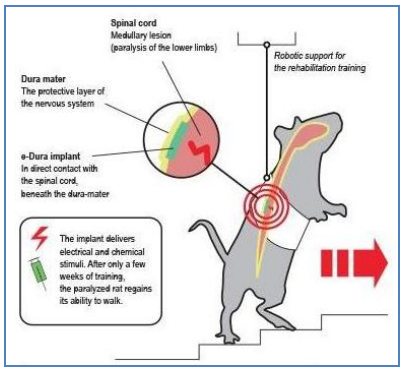
NEWS



page 333

EDITOR'S CHOICE

page 355

PICTURE STATION

REVIEW

COMMON SCIENCE

COVER
The electrical properties of cancer cell surface can attract sufficient efforts to further understand their underlying mechanisms and implications in the clinical settings for diagnosing and treating cancer. See page 346.
Image: BASE illustrating group

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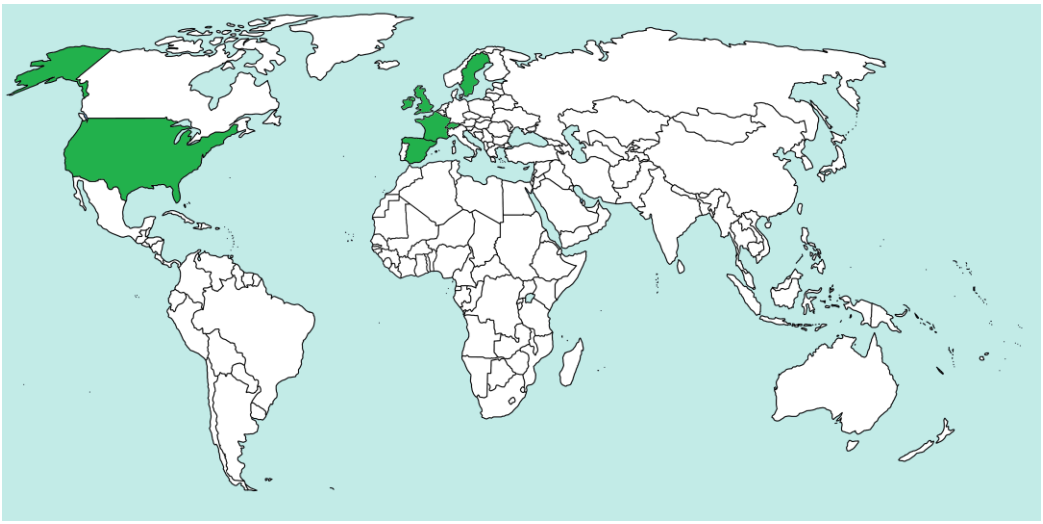
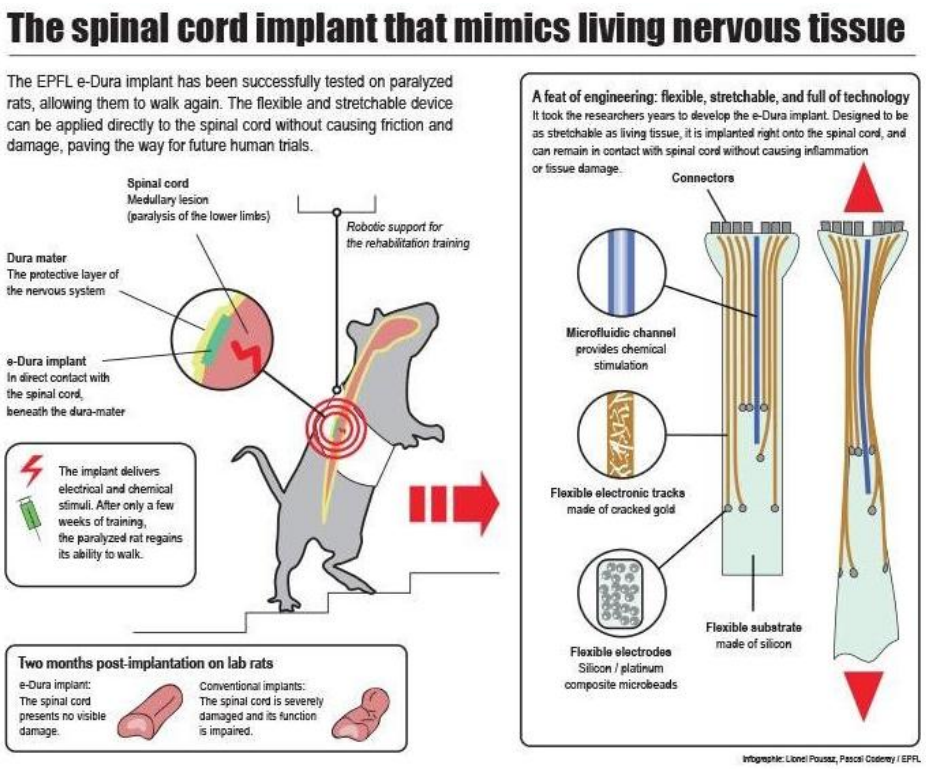
Lausanne, SWITZERLAND

Flexible Implant Will Allow Paralysed Humans to Walk



Last year, researchers at the Ecole polytechnique federale de Lausanne, Switzerland, successfully demonstrated a system that allowed completely paralysed rats to walk again. Using a system of electrical and chemical stimulation, the rats -- whose spinal cords had been completely severed -- were able to once again move their hind limbs. The technology is now one step closer to clinical human trials, with a flexible implant specifically designed to integrate with the patient's spine, minimising the risk of rejection and further damage. The implant, called e-Dura, is designed to be implanted directly onto the brain or spinal cord, underneath the dura mater, the membrane that encloses the brain and spinal cord. Its mechanical properties -- flexible and stretchy -- are almost identical to those of the living tissue enclosing it, vastly reducing the risk of inflammation, friction and abrasion. This is in direct contrast to "surface" implants. These are rigid, which causes frictional inflammation on the surrounding tissues when implanted long-term The team at EPFL has tested the implant in rats and has found that, even after two months, there was no tissue damage or rejection -- in addition, of course, to allowing the rats to walk. This has demonstrated that the implant is both capable of performing its function and compatible with long-term implantation. "Our e-Dura implant can remain for a long period of time on the spinal cord or the cortex, precisely because it has the same mechanical properties as the dura mater itself," said study co-author and EPFL Bertarelli Chair in Neuroprosthetic Technology Stéphanie Lacour. "This opens up new therapeutic possibilities for patients suffering from neurological trauma or disorders, particularly individuals who have become paralysed following spinal cord injury." The flexible silicon implant is covered in cracked gold conduction tracks that stretch with the silicon, while the electrodes, a new composite made of silicon and platinum microbeads, can be pulled in any direction. These conduction tracks and electrodes convey electrical current to the spinal cord, much as the brain does. Meanwhile, a fluidic microchannel in the implant delivers neurotransmitting drugs to reanimate the nerve cells beneath the injured tissue. While this operates in concert to circumvent the injured site on the spine, allowing the patient -- theoretically -- to use their limbs, it can also be used to monitor electrical impulses from the brain in real-time, allowing the researchers to accurately gauge the patient's intention to move before the signal is translated into motion. The human trials may start as ear



ly as June of this year, at a special facility called the called the Gait Platform, housed in the University Hospital of Lausanne, Switzerland.■

Paris, FRANCE

What Can We Do If an Asteroid Threatens Earth?

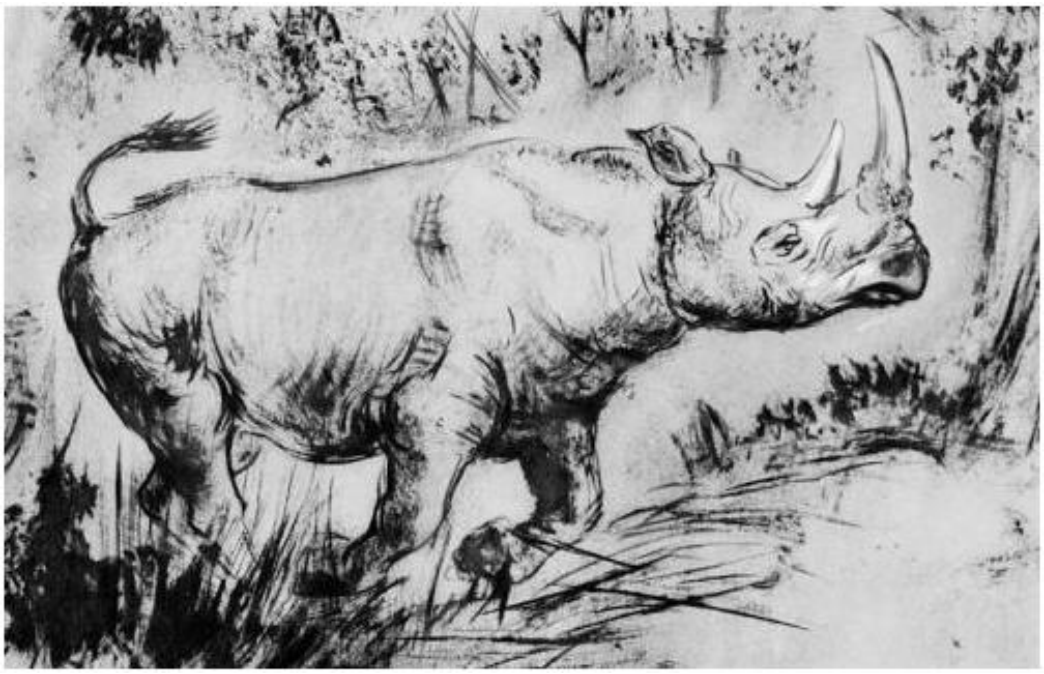
What should humanity do the next time a space rock threatens Earth? European officials recently spent two days figuring out possible ways to respond to such a scenario, with the aim of drawing up effective procedures before the danger actually materializes. The first-of-its-kind simulation considered what to do if an asteroid similar to, or larger than, the one that exploded over Russia in February 2013 — which was about 62 feet (19 meters) wide — came close to Earth. Officials focused on activities ranging from 30 days to 1 hour before a potential impact. "There are a large number of variables to consider in predicting the effects and damage from any asteroid impact, making simulations such as these very complex," Detlef Koschny, head of near-Earth-object activities at the European Space Agency's Space Situational Awareness office, said in a statement. "These include the size, mass, speed, composition and impact angle," he added. "Nonetheless, this shouldn't stop Europe from developing a comprehensive set of measures that could be taken by national civil authorities, which can be general enough to accommodate a range of possible effects." The 2013 Russian meteor explosion, which occurred above the city of Chelyabinsk, helped to bring the asteroid threat into a new realm of public awareness. The shockwave created by the airburst injured 1,500 people; the vast majority were cut by shards of flying glass after windows were shattered. The European authorities performing the new simulation, which took place in late November, took a lesson from the Chelyabinsk event, determining that it would be best to warn the public to stay away from windows and stay in buildings' most secure areas — similar to the advice given during tornadoes. Officials considered what to do if Earth were threatened by an object between 39 feet and 125 feet wide (12 to 38 m) traveling at 28,000 mph (45,000 km/h). ESA and related warning agencies would need to work quickly, they determined, and coordinate with civil protection authorities to give information about where and when the asteroid would likely strike, and what effects would be anticipated. "For example, within about three days before a predicted impact, we'd likely have relatively good estimates of the mass, size, composition and impact location," Gerhard Drolshagen, of ESA's near-Earth-object team, said in the same statement. "All of these directly affect the type of impact effects, amount of energy to be generated and, hence, potential reactions that civil authorities could take."■ By Elizabeth Howell. Originally appeared on Space.com.

Edinburgh, SCOTLAND

Move over Nessie

Scientists have announced the discovery of the fossil remains of a

dolphin-like seagoing reptile on Scotland's Isle of Skye that lived about 170 million years ago and was about 14 feet (4.3 meters) long. The creature, named Dearcmhara shawcrossi, is a member of a group called ichthyosaurs that were among the dominant marine reptiles when dinosaurs ruled the land. Ichthyosaurs, some of which reached monstrous proportions rivaling all but the largest of today's whales, thrived for more than 150 million years until disappearing about 95 million years ago. Dearcmhara, a moderate-sized ichthyosaur, swam in warm, shallow seas during the Jurassic Period, eating fish and squid. Its remains are incomplete but the shape of a bone in its front flippers suggests it may have been an especially strong or fast swimmer, the researchers said. "It is from Scotland, and is the first uniquely Scottish marine reptile ever discovered and studied," said University of Edinburgh paleontologist Steve Brusatte, one of the researchers in the study published in the Scottish Journal of Geology. "Many other marine reptile fossils have been found in Scotland, but the vast majority of these have disappeared into private collections or been sold. This new specimen finally breaks the impasse: it was found by a private collector who did a great thing, donated it to a museum and worked with scientists," Brusatte added. Amateur fossil hunter Brian Shawcross found the fossils on a beach in the northern part of the Isle of Skye in 1959 and donated them in the 1990s, researchers said. The genus name Dearcmhara (pronounced "jark vara") is Scottish Gaelic for "marine lizard." The species name honors Shawcross. "It is important to emphasize how grateful we are that Brian donated the bones he found all those years ago," added paleontologist Neil Clark of the University of Glasgow's Hunterian Museum, which received the fossils. The discovery sheds light on a span of the Jurassic regarded as nearly a black hole in the marine reptile fossil record, Brusatte said. Scotland is one of the few places with fossils from that time. Other fossils indicate Dearcmhara lived alongside members of another branch of marine reptiles called plesiosaurs, known for long necks and paddle-like flippers. The elusive Nessie is commonly portrayed as looking like a plesiosaur.■ By Will Dunham, first edited by Eric Beech and reedited by Julia Park)



Liverpool, UK

Were the Ice Age Environments Reconstructed through Extinct Rhino's Eating Habits?

A study into the feeding behavior of two extinct European rhinoceros species has revealed an unexpected survival strategy for a mammalian family of the Ice Ages. The new findings published in the journal Quaternary Science Reviews showed that the rhinos had the ability to change their diet regardless of their dietary specialization, for example when the climate changed. Based on these surprising findings, reconstructions of the Ice Age environments, which were partly based on the diet assumed for these rhinoceroses, must also be reconsidered. Liverpool John Moores University's Dr Eline van Asperen from the Research Centre in Evolutionary Anthropology and Paleoecology, worked alongside Ice Age paleontologist Professor Dr Ralf-Dietrich Kahlke of the Senckenberg Research Station of Quaternary Paleontology in Weimar (Germany) to investigate the feeding behavior of the extinct European “forest” rhinoceros Stephanorhinus kirchbergensis and “steppe” rhinoceros Stephanorhinus hemitoechus. Using a wide range of find spots, the German-British team established that the extinct rhinoceros species followed their food preferences when food resources were plentiful and varied, but when available food sources were more uniform, they were able to skip their 'ecological imprint' and to take what was available. They concluded that the feeding habits of the so-called 'forest' and 'steppe' rhinoceros did not necessarily reflect the habitats from which they derive

their names. Dr van Asperen and Professor Kahlke studied the fossil teeth of more than 200 individual rhinoceroses of between 350,000 and 100,000 years old from a wide range of find spots in Germany and the United Kingdom. They reconstructed the food spectrum of these extinct animals using the “mesowear method”, which is based on the fact that different foodstuffs lead to different wear patterns on the teeth. The extant African black rhinoceros preferentially subsists on soft plant foods – its diet consists mainly of leaves, which it strips off branches and twigs. The African native white rhinoceros, in contrast, is fully adapted to eating coarse grass. For the extinct European rhinoceros species Stephanorhinus kirchbergensis and Stephanorhinus hemitoechus , a similarly specialized feeding strategy had been assumed, but the research found that they were considerably more flexible in their diet in extreme conditions. The “forest” rhinoceros Stephanorhinus kirchbergensis , which originated in Asia, was larger than all extant rhinoceroses and "both the shape of its teeth and the way its head is connected to its vertebral column indicate a preference for feeding in forests", says Kahlke. The somewhat smaller 'steppe' rhinoceros Stephanorhinus hemitoechus , in contrast, held its head much lower – this, as well as the shape of its teeth, point towards a dietary specialization for coarser, ground-level vegetation. Both species evolved during a time of relatively long, stable warm periods, which created favourable conditions for the development of dietary specialists. "We therefore assumed that these animals would have had a strong tie with the available resources of forest or steppe", explains Dr van Asperen. But the research found that both rhinoceros species could eat both soft leaves and coarser grasses. The study has implications for the reconstruction of Ice Age environments. Previously, the presence of many “forest” rhinoceros fossils at a find spot was taken as evidence that the find spot was formed in a forested environment. But it now appears that 'forest' rhinos could also survive in more open environments. The study provides food for thought for conservationists, who need to consider the option that animals already may be surviving on the margins of their flexibility in suboptimal environments.■

Lund, SWEDEN

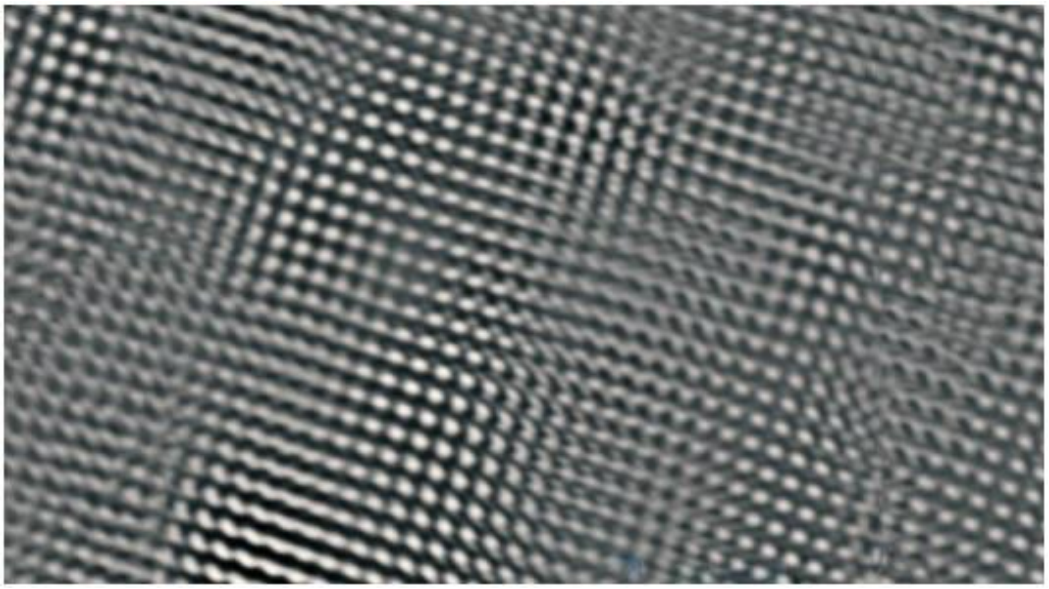
Do Viruses Make Us Smarter?

A new study from Lund University in Sweden indicates that inherited viruses that are millions of years old play an important role in building up the complex networks that characterise the human brain. Researchers have long been aware that endogenous retroviruses constitute around five per cent of our DNA. For many years, they were considered junk DNA of no real use, a side-effect of our evolutionary journey. In the current study, Johan Jakobsson and his colleagues show that retroviruses seem to play a central role in the basic functions of the brain, more specifically in the regulation of which genes are to be expressed, and when. The findings indicate that, over the course of evolution, the viruses took an increasingly firm hold on the steering wheel in our cellular machinery. The reason the viruses are activated specifically in the brain is probably due to the fact that tumours cannot form in nerve cells, unlike in other tissues." We have been able to observe that these viruses are activated specifically in the brain cells and have an important regulatory role. We believe that the role of retroviruses can contribute to explaining why brain cells in particular are so dynamic and multifaceted in their function. It may also be the case that the viruses' more or less complex functions in various species can help us to understand why we are so different", says Johan Jakobsson, head of the research team for molecular neurogenetics at Lund University. The article, based on studies of neural stem cells, shows that these cells use a particular molecular mechanism to control the activation processes of the retroviruses. The findings provide us with a complex insight into the innermost workings of the most basal functions of the nerve cells. At the same time, the results open up potential for new research paths concerning brain diseases linked to genetic factors. "I believe that this can lead to new, exciting studies on the diseases of the brain. Currently, when we look for genetic factors linked to various diseases, we usually look for the genes we are familiar with, which make up a mere two per cent of the genome. Now we are opening up the possibility of looking at a much larger part of the genetic material which was previously considered unimportant. The image of the brain becomes more complex, but the area in which to search for errors linked to diseases with a genetic component, such as neurodegenerative diseases, psychiatric illness and brain tumours, also increases".■

Boston, USA

Researchers Discover a Universal Law of Superconductivity

The immutable laws that govern our universe – such as those that reign over the observable world in classical mechanics and those that rule the atomic physics world – are at the core of all of our scientific principles. They not only provide



consistent, repeatable, and accurate rules that allow calculations and experiments to be tested or verified, they also help us make sense of the workings of the cosmos. MIT researchers claim to have discovered a new universal law for superconductors that, if proved accurate, would bring the physics of superconductors in line with other universal laws and advance the likes of superconducting circuits for quantum and super low-power computing. Superconducting materials have no electrical resistance at temperatures close to absolute zero, which means that very small amounts of energy are required to induce electrical currents in them. Devices, such as computer processors, built from these materials would theoretically be expected to use many hundreds of times less energy than conventional circuits. However, until recently, the correlation between the physical and electrical parameters of superconductors has been largely based on assumptions from standard theoretical physics and no one single law on these functions had been previously proven. The new mathematical relationship discovered by the researchers involving material thickness, temperature, and electrical resistance, on the other hand, so far appears to hold true in all superconductors. Prior to the MIT research, other theoretical work had previously indicated that the critical operating temperature in a superconductor was a function of the thickness of the film from which it was made or its measured electrical resistance at room temperature. However, when the team grew superconductors from niobium nitride atoms, these theories did not seem to hold true. "We saw large scatter and no clear trend," said Yachin Ivry, a postdoctoral researcher in MIT's Research Laboratory of Electronics. "It made no sense, because we grew them in the lab under the same conditions." To attempt to understand this anomaly between theory and practice, the researchers decided to conduct a number of experiments with the growing of the superthin film to see if they could produce more consistent results. To do this, they kept one of two parameters constant: the thickness of the material or its "sheet resistance" (the material's resistance per unit area). They then measured any changes in critical temperature whilst varying either of these parameters. As a result of this work, a pattern of repeatable behavior resulted. The team was able to show that sheet thickness (d) multiplied by the critical temperature (Tc) equaled a constant divided by sheet resistance (Rs) raised to a particular power, thereby providing the universally-applicable thin-film superconductivity relationship formula: dTc(Rs). "We were able to use this knowledge to make larger-area devices, which were not really possible to do previously, and the yield of the devices increased significantly. Thin films are interesting scientifically because they allow you to get closer to what we call the superconducting-to-insulating transition," said Ivry. "Superconductivity is a phenomenon that relies on the collective behavior of the electrons. So if you go to smaller and smaller dimensions, you get to the onset of the collective behavior." The researchers believe that application of their research will provide greater insights into thin-film superconductivity, which could see improvements in the likes of super-sensitive photodetectors and quantum computing semiconductors. "This is very convenient for technical applications, because there is a lot of spreading of the results, and nobody knows whether they will get good films for superconducting devices," says Claude Chapelier, a superconductivity researcher at France's Alternative Energies and Atomic Energy Commission. "By putting a material into this law, you know already whether it's a good superconducting film or not." By Colin Jeffrey, Source: MIT.■

Paris, FRANCE

Metabolism Pointer for Quitting Smoking

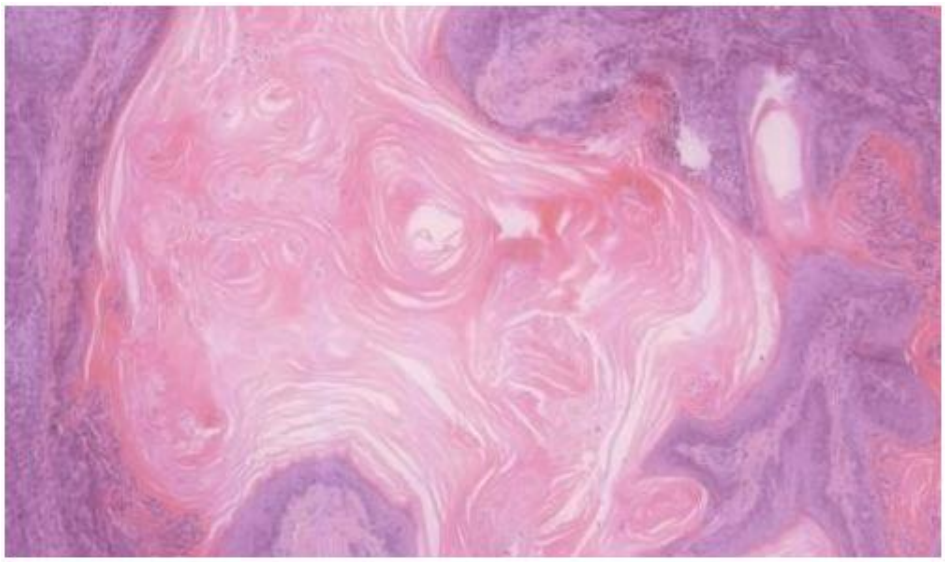
How quickly a smoker breaks down nicotine is a guide to which therapy is best for kicking the habit, according to research published Monday. Most smokers who try to give up tobacco fail within the first week, so matching them to the best treatment is essential, its authors said. Previous research has found a link between tobacco crav-

ing and levels of an enzyme called CYP2A6 which breaks down nicotine. The faster the nicotine is metabolised, the likelier it is that the smoker will want to light up again soon, and the harder it will be to quit. Scientists in the United States and Canada used a biomarker -- the speed at which CYP2A6 does its job -- to see whether nicotine patches or a non-nicotine replacement drug called hantix or Champix) were more effective. Smokers who broke down nicotine quickly -- most smokers, in fact -- were twice more likely to quit if they used varenicline than if they used patches, they found. They also had a better chance of staying of tobacco six months later. Slower metabolisers found nicotine patches to be as effective as varenicline, but without that drug's side effects. The studies covered 1,246 smokers who wanted to quit, divided roughly equally into fast and slow metabolisers. The smokers were randomly assigned to an 11-week course that comprised either a nicotine patch plus a dummy pill, varenicline plus a dummy patch or a dummy patch and a dummy pill. The study did not cover electronic cigarettes, which some advocates say are a useful tool for giving up smoking. The results should lead to a simple blood test for nicotine metabolism so that doctors can better advise patients, the authors hope. "As many as 65 percent of smokers who try to quit relapse within the first week," said Caryn Lerman, a professor of psychiatry at the University of Pennsylvania, who co-led the study. "Matching a treatment based on the rate at which smokers metabolise nicotine could be a viable clinical strategy to help individual smokers choose the cessation method that will work best for them." Around six million deaths annually can be attributed to tobacco, and smoking inflicts around $200 billion (169 billion euros) in health costs annually, the paper said.■

Madrid, SPAIN

Genetic Pieces of Bladder Cancer

Notch genes are a double-edged sword: in some cancers they have a harmful effect because they promote tumor growth, whilst in others they act as tumor suppressors. The reason is still unclear, making it impossible to predict the behavior of Notch within each tumor, and complicating its use as a drug target. Now, CNIO researchers clear this dilemma up for bladder cancer, in which it exerts an anti-tumor effect. This result calls for caution when using therapeutic strategies based on the deactivation of Notch, because they could increase the risk of developing bladder cancer. The study, published by The Journal of Clinical Investigation, is a joint effort between CNIO's Tumor Suppression and Epithelial Carcinogenesis Groups, led by Manuel Serrano and Francisco X. Real, respectively. In addition to clarifying the role that Notch plays in bladder cancer—the fifth most frequent cancer among men in developed countries—the authors offer clues to understand the dual function of this family of genes. "Our analysis of Notch mutations in bladder cancer, mouse models, cell-based assays



and human cancer samples offer solid evidence that the Notch pathway plays a relevant role as a tumor suppressor in bladder cancer," they write. This result is not a surprise. Many of the tumors in which Notch acts as a suppressor are cancers that arise in squamous cells, which are found in different organs, such as the esophagus or the skin. The urinary bladder can give rise to squamous cell cancer, so "we hypothesized that Notch could act as a suppressor in this tissue," explains the article. The confirmation of this hypothesis supports the idea that Notch intervenes in the architecture of the so-called stratified epithelia, in which cells grow in superimposed layers —a type of growth that also takes place in the bladder. The researchers from the two CNIO groups brought together their strength and expertise. The Epithelial Carcinogenesis Group had sequenced the exome—the part of the genome that is translated into proteins—for 17 bladder cancers, and detected Notch mutations. The Tumor Suppression Group provided mouse models for the genetic inactivation of Notch, specifically in the bladder. The study concludes with a call for caution: "Our group as well as other investigators had previously described the anti-tumor effects of pharmacologic inhibitors of Notch in pre-clinical models [of lung adenocarcinoma, where Notch is oncogenic]; our current data suggest that caution must be taken in the clinical application of non-specific Notch pathway inhibition, because it could increase the incidence of squamous-type tumours, like in the bladder."■

BASE

THE BONOI ACADEMY OF SCIENCE & EDUCATION

Call for Subcommittee Members

The Bonoi Academy of Science & Education (BASE) is composed of 20 different scientific and educational divisions. All these divisions are consisted of Director, Co-Director, Standing Committee, and Office Members. Some of the divisions are enrolling above positions. If you are interested in science or education work and if you think that is of great value for your career development, please send us your application asap. Given the BASE is a non-profitable organization, these positions then are also non-profitable, the BASE is not responsible for the salary or any other benefits. If you are approved as a member of one of the subcommittees, you automatically become a member of the BASE, which means you do not need to pay for the membership fees during the term. Of course, you are also eligible for applying for the BASE awards and funding, and also suitable for the member benefits. Come on with us to spread science knowledge to the far corner of the world by education.

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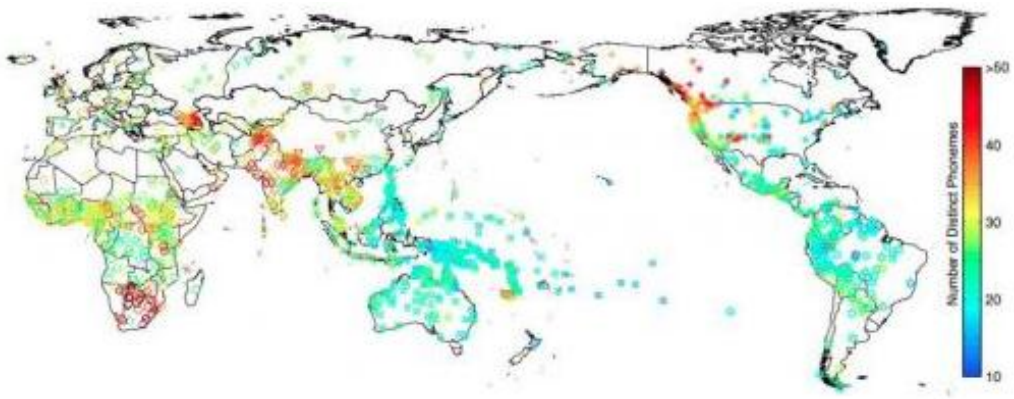
HUMAN DEVELOMENT

Probing the Deep History of Human Genes and Language



Researchers analyzed distinct sounds — phonemes — in more than 2,000 languages around the world alongside genetic markers from more than 200 populations to uncover geographic patterns of how languages differ. Producing new insights into the evolution and development of human populations around the globe is no easy task, but scientists can draw on multiple sources of data to do it. In a new study, Sohini Ramachandran and colleagues at Stanford University and University of Manitoba analyzed troves of data on genetics and distinct sounds in language—phonemes—to discern important patterns. Among the findings published in *Proceedings of the National Academy of Sciences*, is that genes and languages both vary more as geographic distance increases. The analysis showed there are distinct geographic patterns, or axes, of the greatest differences. The data also reflect how languages and genes evolve differently, for instance among isolated populations. Ramachandran, assistant professor of ecology and evolutionary biology, discussed these and other insights with writer David Orenstein. Fields that study the human past, especially ancient human history, have to draw on multiple disciplines and lines of evidence in order to confirm and calibrate observed signatures in data, since we can't truly know all events in human history. Because language is inherited 'vertically' [from parents to children] like genes, and also changes 'horizontally' based on contact among populations, many researchers in genetics interpret analyses of DNA from different populations in the context of the languages the study populations speak. This kind of interdisciplinary work is what initially drew me to studying human evolution. We saw that axes of differentiation in both our linguistic and genetic dataset corresponded, meaning that differences in both datasets of very different types of markers were geographically distributed quite similarly. One very interesting contrast we saw between languages and genes had to do with isolated populations: an isolated population loses genetic diversity rapidly, as individuals marry within the population; in contrast, we saw a range of variation in linguistic markers for languages that are geographically isolated (have few neighboring languages). Some languages that are isolated lose complexity and others gain complexity and innovate new sounds. This makes me wonder whether contact among populations homogenizes their languages in some way so people can understand each other. We found that linguistic markers do not hold signatures of the human expansion out of Africa, which is not surprising due to the rate at which languages changes and can be influenced by neighboring languages. To be precise, genes tell us that the people living today with the most genetic diversity currently live in Southern Africa (like the San bushmen) and that modern humans emerged in Africa, but we don't know where the geographic origin of our species was precisely based on genetic data. The language analysis did not reveal this African origin because language changes in a complex way, much differently from genes where we have a good sense of the mutation process. In my conversations with different linguists, including those at Brown who generously listened to me present our ideas multiple times, the rate at which language mutates, and which linguistic markers are more likely to change than others, seems to be an open question. These axes, which look for directions along which a dataset is most differentiated, tell us about axes along which humans likely did not migrate a great deal. For example, migration north/south in Africa would mean moving across climate regimes; we also know populations are quite different across latitudes in Europe and we see that for both our language datasets and genetic datasets. We learn more from using both data types together and analyzing them using similar methods than we would have learned from either type alone. One signal we saw loud and clear in this study is how much geographic distance affected our ancestors' genes and languages; geographic distance predicts differentiation in both data types, underscoring that there are still deep signatures of ancient migrations in our genomes and cultures today.■

PNAS 2015;
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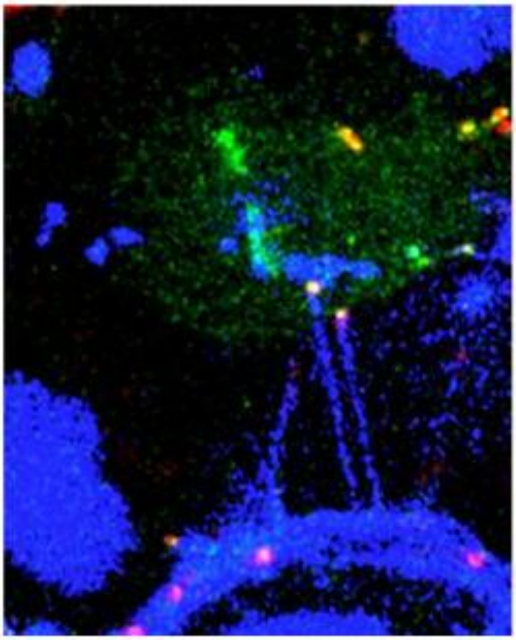
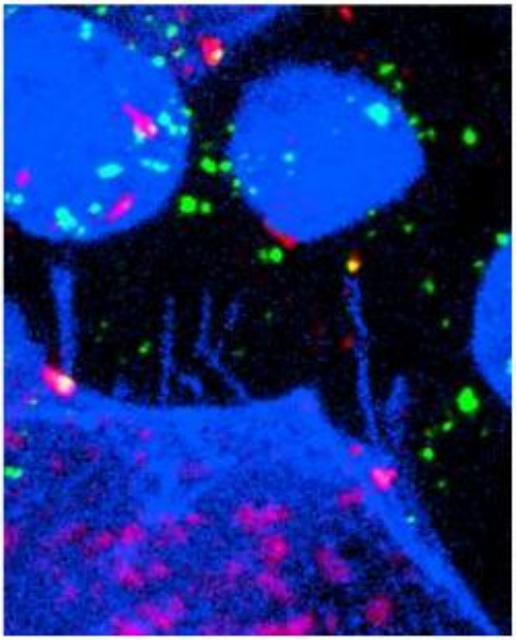
CELLULAR BIOLOGY

How Cells Communicate





During embryonal development of vertebrates, signaling molecules inform each cell at which position it is located. In this way, the cell can develop its special structure and function. For the first time now, researchers of Karlsruhe Institute of Technology (KIT) have shown that these signaling molecules are transmitted in bundles via long filamentary cell projections. Studies of zebrafish of the scientists of the European Zebrafish Resource Center (EZRC) of KIT revealed how the transport of the signaling molecules influences signaling properties. A publication in the Nature Communications journal presents the results. Organisms, organs, and tissues are complex three-dimensional systems that consist of thousands of cells of various types. During embryonal development of vertebrates, each cell requires information on the position at which it is located in the tissue. This position information enables the cell to develop a certain cell type for later execution of the correct function. This information is transmitted via signal molecules, so-called morphogenes. These morphogenes are not homogenously distributed in the tissue, their concentration varies. Various concentrations activate various genes in the target cell. The cells in the developing central nervous system receive their position information from signal molecules belonging to the family of Wnt proteins. The concentration of Wnt proteins determines whether a cell differentiates to a cell of the forebrain or of the afterbrain. "Distribution of these signal molecules has to be controlled precisely," Dr. Steffen Scholpp, head of a research group of the KIT Institute of Toxicology and Genetics (ITG), explains. "Smallest changes of the concentration or the transport direction may cause severe damage, such as massive malformations during embryonal development or formation of cancer." For the first time now, the working group of Dr. Steffen Scholpp has shown that the Wnt proteins are transmitted specifically via long cell projections, so-called filopodia. In the Nature Communications journal, the scientists report that the signaling factors are loaded on the tips of the filopodia only. In this way, signaling can start immediately upon contacting. The signaling factors bind to the corresponding receptors of the target cell and induce the correct cell response. "Now, the source cell can decide precisely which target cell receives how much signaling protein at which time," Scholpp explains. The KIT researchers study zebrafish and human cell lines and succeeded in reproducing or reducing the filopodia and analyzing the resulting changes of signaling properties of the Wnt morphogenes.■

Nat Commun 2015; Doi: 10.1038/ncomms6846

BIOLOGY

New Species of Legless Amphibian in Cambodia's Cardamom Mountains

The new species, Ichthyophis cardamomensis, is a caecilian, an order of limbless amphibians often mistaken for snakes, with larger species known to grow to 1.5 meters in length. This discovery, at only 30 cm, is linked to the continuing ground-breaking work at the Centre for Biodiversity Conservation (CBC) in Phnom Penh, a joint initiative of Fauna & Flora International (FFI) and the Royal University of Phnom Penh (RUPP). Leading Cambodian FFI herpetologist Neang Thy has been researching amphibians and reptiles since 2003 and is very excited that the I. cardamomensis species has been officially confirmed. This discovery is one of three new species of unstriped Ichthyophis caecelians (the other two were found in Vietnam) introduced in the 'New Ichthyophis species from Indochina' paper published recently in the Organisms Diversity & Evolution scientific journal (published by the Society for Biological Systematics). Between 2009 and 2011, Cambodian species samples were collected by Neang Thy and Dr Lee Grismer from the US La Sierra University with final confirmation from lead paper author, Dr Peter Geissler from the State Museum of Natural History Stuttgart,

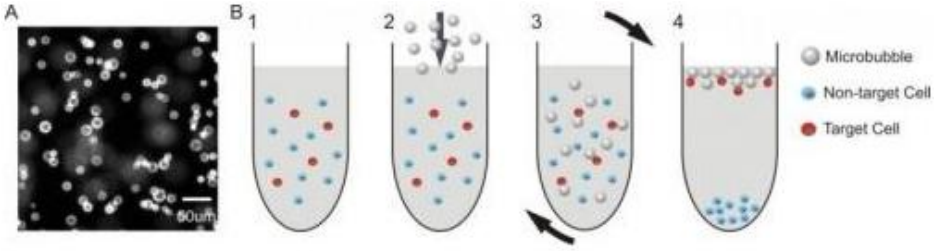
Germany. The I.cardamomensis species is only the second caecilian species ever discovered in Cambodia. The other is the striped Koa Tao Island caecilian, I. kohtaoensis, which is also found in, Laos, Myanmar, Thailand, and Vietnam. "These discoveries are important to demonstrate that much of Cambodia's biodiversity remains unknown and unstudied by science, and many more areas need to be searched," Thy said. The forested Cardamom Mountains Range represents some of the largest remaining areas of habitat for more than 80 threatened species, including Asian elephant and gaur. Thy said in recent years the Cardamom region had revealed its extensive reptile and amphibian diversity, including frogs, turtles, lizards and crocodiles. "We are still learning about this area and the animals in it, since it was a region formerly held by the Khmer Rouge and the mountains were closed to researchers until the 1990s," he said. "The Cardamom region it is under threat from logging, land concessions, and other habitat destruction, and the danger of any new species, including the new caecilian, is that they may be discovered one year and go extinct the next." Caecilians have a valuable role in the ecosystems of tropical and subtropical regions, including providinga food source for the red tailed pipe snake Caecilians are a difficult group to describe as they look so similar, and there are few caecilian experts, so comprehensive morphological and molecular (DNA) analyses is needed to recognise a new species. Zoologist Dr Peter Geissler said caecilians of the genus Ichthyophis were some of the most poorly known amphibian taxa within Southeast Asia. "Three distinct unstriped Ichthyophiid species – I. cardamomensis from western Cambodia, I.catlocensis from southern Vietnam, and I.chaloensis from central Vietnam are now described as new species, almost doubling the number of Ichthyophis species known from the Indochinese region, " he said. Caecilians are best described as snake or worm-like amphibians that lack limbs. They have the typical amphibian skin that clearly differs from snakes, and they have skull and bones which differs from worms.■ By Louisa Mckerrow.

Organ Divers Evolut, 2015;15: 143

BIOTECHNOLOGY

Fast sorting of CD4+ T cells from whole blood using glass microbubbles

Human immunodeficiency virus (HIV) disease represents a global health problem concern in the world especially in many areas of Africa. According to the Joint United Nations Programme on HIV and AIDS (UNAIDS), there were 24.7 million people living with HIV in sub-Saharan African in 2013 but only 37% of the patients were treated. Despite the support of global efforts to fight HIV, the outcome has not been successful because the cost of HIV medications is still an obstacle to getting most patients on therapy in the developing countries where the majority of the whole populations have very low incomes compared to the western countries. For human immunodeficiency virus (HIV) infected patients the number of CD4+ T lymphocytes in peripheral blood is an important maker for monitoring disease progression of AIDS and treatment efficacy. But the standard methods for enumerating CD4+ T cells by using fluorescence-activated cell sorting (FACS) or magnetic-activated cell sorting (MACS) are expensive and not easily accessible in remote areas. Our report shows an alternative method for isolating CD4+ T cells which can be used for CD4+ T cell enumeration. One critical advantage of glass microbubbles is their reduced cost. These glass microbubbles have been mass-produced for use in many industrial applications including insulation, construction, paints, and transportation. The surface of the glass microbubbles can also be modified for attaching a variety of biochemicals to, using readily available protocols developed for glass substrate. In addition the buoyancy of the glass microbubbles allows for the capturing and separation of target cells from the unwanted cells by a simple "flip tube" motion. Together



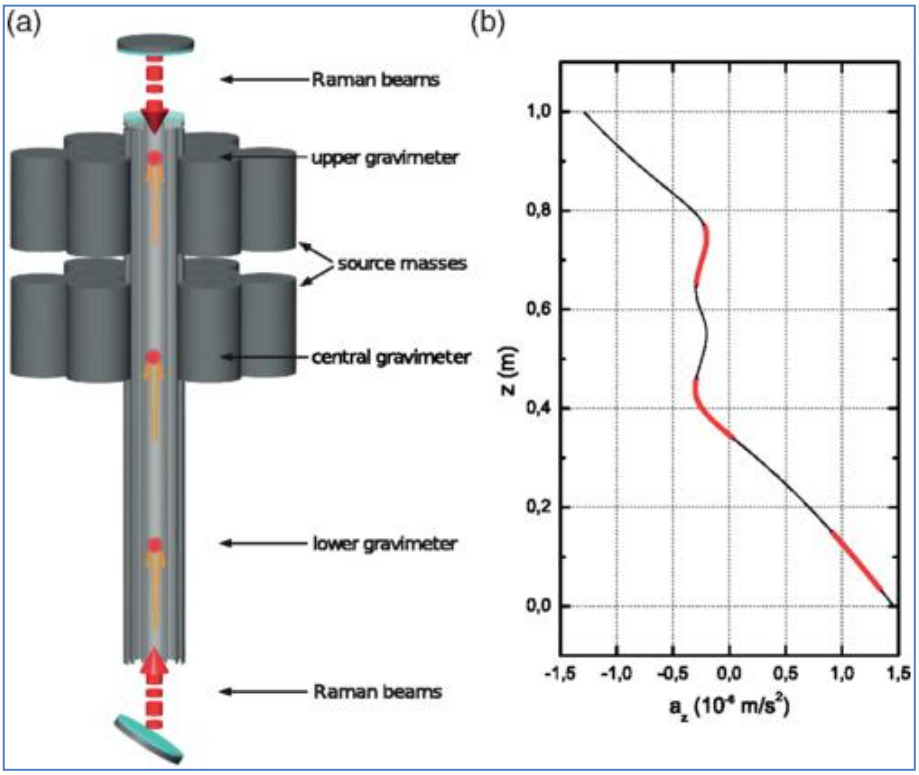
these features make our technology very attractive to the development of low-cost point-of-care devices for HIV monitoring. There are currently huge inequities in HIV disease burden between developed and developing countries due to the fact that in many developing countries the health care is facing tremendous challenges from not having sufficient financial resources to support the health care of HIV patients. The production of new health technologies may help to bridge this gap by lowing the cost of medical care to provide better treatment to the patients.■

TECHNOLOGY 2015; Doi: 10.1142/S2339547815500016

PHYSICS

First Direct Measurement of Gravity's Curvature

A team of researchers working in Italy has successfully conducted an experiment to directly measure gravity's curvature for the first time. In their paper published in the journal Physical Review Letters, the team describes their work and note that what they have accomplished could lead to an improvement in G, the Newtonian constant of gravity. Over many years, scientists have developed more sophisticated ways to measure gravity, one of the latest is to use atom interferometry—it enables distance measurement with very high precision and works by exploiting the quantum-mechanical wavelike nature of atoms. Up till now researchers have been able to measure the changes in gravity as altitude increases, for heights as little as a few feet, creating a gradient. In this new research the team has found a way to measure the change in gravity that is produced by a large mass. This change in the gradient is known as gravity's curvature. To directly measure the change in a gradient, the team used measurements made at three different heights. Measuring gravity at two locations close to one another can give the gradient as the measured difference of the two divided by the distance between them. Measuring gravity at three locations allows for calculating the rate of change, or curvature—an idea for an experiment to carry out this measurement was first proposed back in 2002. The experiment conducted by the team in Italy is based on that proposal. To allow for measuring gravity at three locations all at the same time, the team created three plumes of ultracold atoms at three different heights inside of a one meter pipe. The top half of the piper was surrounded by tungsten alloy weights to cause an increase in variation of the gravitational field. The atoms were irradiated with pulses from a laser to cause them to separate the plumes into two parts, one that absorbed photons and a second that was left in a ground state. The additional momentum caused the atoms in the first group to fall a different distance over a measured time period, which led to a difference in quantum wave cycles that elapsed between the two. The team then added two more wave pulses to cause the two groups to recombine, which allowed them to interfere. Measuring the interference allowed for calculating the variations in gravitational acceleration and curvature, which turned out to be 1.4×10^{-5} s^{-2} m^{-1}, as predicted. The team believes their method should prove useful for geologic and mapping work as well as improving the measurement of G.■ By Bob Yirka.



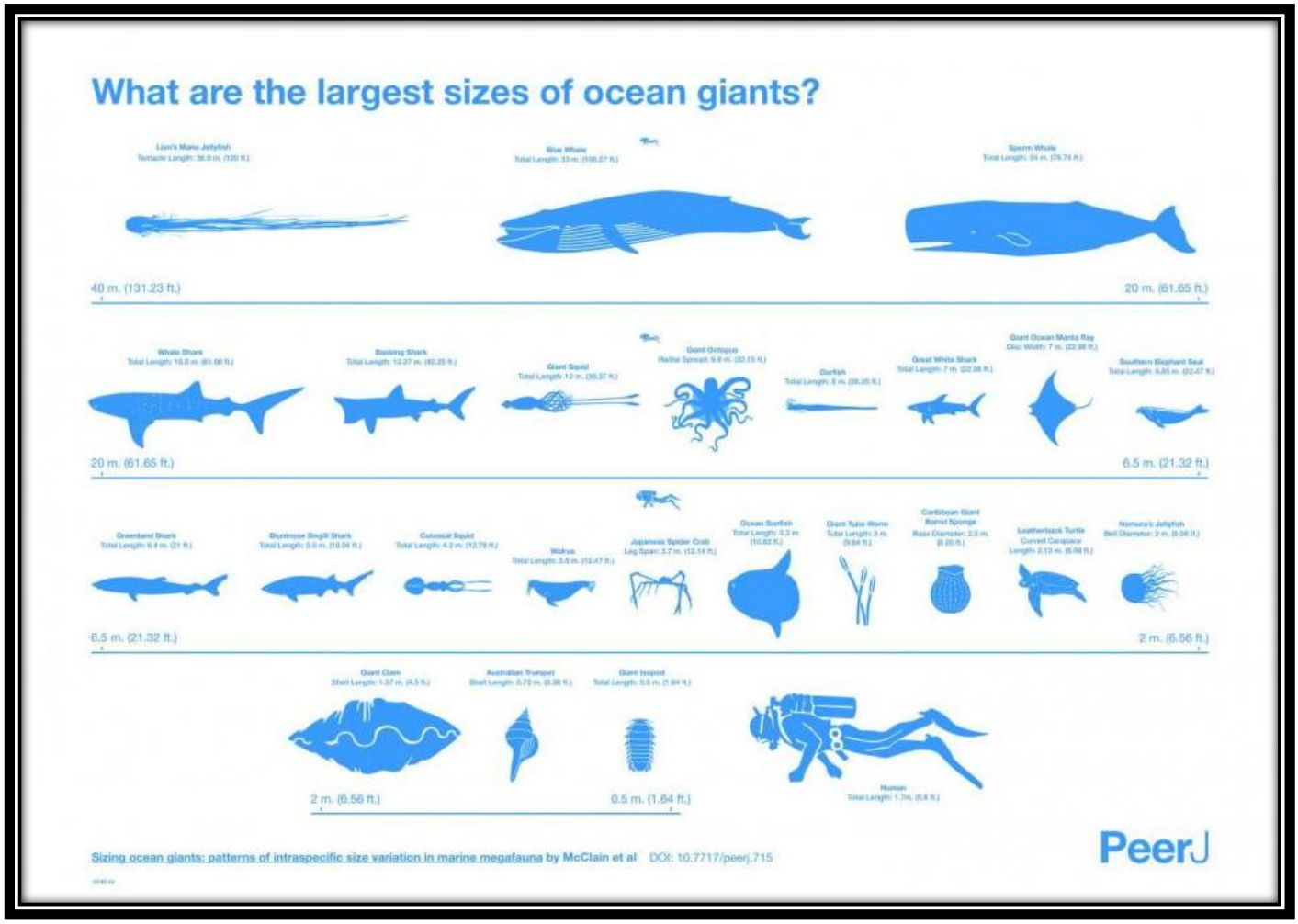
Phys Rev Lett 2015; Doi: 10.1103/PhysRevLett.114.013001


help those in need...

Stop wasting foods

Accurate Size of Largest Sea Creatures

By Douglas Main (2015, USA)

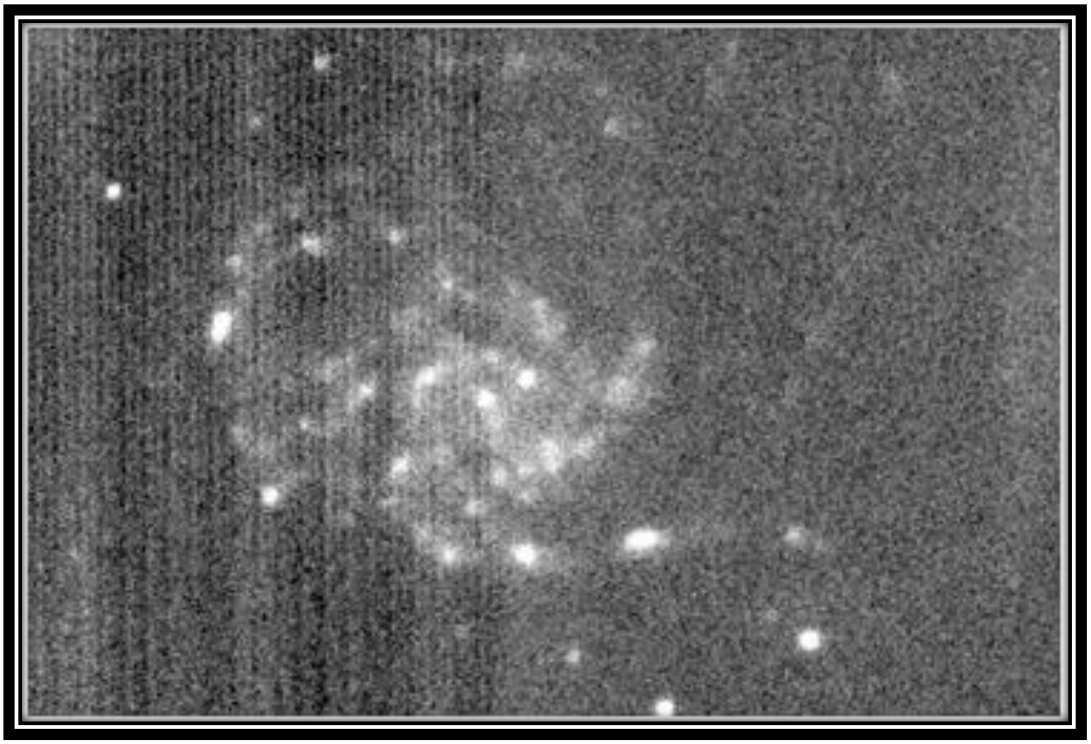


We humans like to tell tall tales. Literally. When people—even scientists—record and communicate the size of various animals, they tend to exaggerate the beasts' size. Looking to set the record straight, scientists have put together a comprehensive survey of past studies and verifiable documentation to determine the accurate size of a range of marine animals, from crabs to whales. They found that in many cases that the alleged record size for a species was significantly larger than anything that could be scientifically validated. "It's sort of human nature to make everything bigger, and we are poor observers of size in general," says study lead author Craig McClain, a marine biologist at Duke University. "I don't think there were any examples of animals being larger in reality than what people had thought—in almost every case they were smaller, or the same, as reported previously." For example, giant squid are often referred to in the popular media and old studies as growing up to 49 feet or even 59 feet, says McClain, who is also the assistant director of the National Evolutionary Synthesis Center. This is almost certainly a significant overestimate, and may result from previous measurements being made on dead animals that washed ashore; tentacles can loosen and stretch out as they begin to decay, he says. Instead the authors wrote in the study, "we feel that the longest scientifically verified giant squid is 12 [meters]," or 39 feet. Of course, that's still impressive, he adds. They found similar overestimates for other oceanic beasts. They came up with the new, more accurate records by consulting recent peer-reviewed studies, polling scientists around the world, and even looking at measurements of specimens sold on eBay. Some of these latter numbers tend to be quite accurate—people who collect giant mollusks, for example, are very precise about measuring length as this directly impacts price, McClain says. And dealers who fudge size statistics don't tend to survive, he adds. So check out the above image in case you want to know the accurate record size for the ocean's behemoths—whether it was the 120-foot lion's mane jellyfish or the 4.5-foot-wide giant clam. The scientists' results are also published online in the journal *Peer J*.■


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

Pinwheel Galaxy from Lunar Surface

By Leonard David (2015, USA)



China's first lunar lander Chang'e 3 remains is still operation after more than a year on the moon, and has captured a photo of a distant galaxy as seen from the lunar surface. According to the Lunar Enterprise Daily, the Chinese lander observered the Spiral Galaxy M101, also known as the Pinwheel Galaxy, on Dec. 2 using its Lunar Ultraviolet Telescope (LUT). The galaxy is about 21 million light-years from Earth. The Chang'e 3 image will be "refined further" by the National Astronomical Observatories of China (NAOC) in Beijing. Chang'e 3's astronomical observations from the moon have been done in collaboration with the International Lunar Observatory Association – an interglobal enterprise incorporated in Hawaii – and the University of Hawaii at Hilo, and the Canada-France-Hawaii Telescope Lunar Astronomy Team on Hawaii Island According to Walter Kiefer of the Lunar and Planetary Institute: "The Chang'e 3 image is not the first galaxy imaged from the moon. During the Apollo 16 mission in 1972, astronauts John Young and Charlie Duke operated the Far UV Camera/Spectrograph from the lunar surface. One of the astronomical targets that they imaged was the Large Magellanic, which is a satellite galaxy to our Milky Way Galaxy. According to the Apollo 16 Preliminary Science Report, the imagery of the Large Magellanic Cloud revealed evidence of active star formation regions." The Chang'e 3 mission marked China's first robotic lunar landing in mid-December 2013. It later deployed Yutu moon rover, China's first rover.■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Historical and Practical Perspective of the Unique Surface Electrical Properties of Cancer Cells

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Historical and Practical Perspective of the Unique Surface Electrical Properties of Cancer Cells

Dong Wang,*,Δ Wen-ying Wang,† Zheng Cui,‡ Dong-lu Shi ¶

SUMMARY The fact that cancer cells have abnormal surface electrical charges has been discovered for more than half a century and yet it still has not been understood well despite of enormous efforts in cancerous research. Due to the lack of effective tools for the real-time measurement of electrical properties of individual live intact cells, researches for cancer cellular electricity has been plagued with much less understanding than other cellular signaling mechanisms. We herein review the major historic events of discovering the abnormal surface electrical properties of cancer cells. Although it is still difficult to fully understand this unique property of cancer cells, some applications using the unique surface electrical property of cancer cells, such as the polycation functionalized nanomaterials as the targeted anti-cancer drug delivery system and the utilization of the positively charged host defense peptides as universal anti-cancer drugs, are also reviewed. With the appearance of innovative techniques, the electrical properties of cancer cell surface can attract sufficient efforts to further understand their underlying mechanisms and implications in the clinical settings for diagnosing and treating cancer.■

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ELECTRIC PROCESS is the basis of the biological process, and also undergoes the strong association with the health and different types of diseases (1). Albert Szent-Györgyi, the Nobel Prize laureate in Physiology and Medicine in 1937, indicated in his book *Bioelectronics* that biochemical explanations alone fail to explain the role of electricity in cellular regulation (2). He believed that the cells possess electrical mechanisms and use electricity to regulate and control the transduction of chemical energy and other life processes. Electromagnetic fields have information and communication roles in

that they are employed by living organisms as information conveyors from the environment to the organism, within the organism and among organisms (3). The importance of the widespread use of electricity in biological function cannot be overstated. All the important biological functions, such as the transduction of information from the environment to the organism, within the organism and among organisms, the regulation of cellular volume, the transport of metabolites, the control of the cell cycle, cell proliferation, cell migration and tissue regeneration etc.(4) are intimately linked to the flow of bioelectric signals. Normal cells possess the ability to communicate information inside themselves and between other cells through a series of well-regulated biological electronic circuits and wireless communication mechanisms. Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to unregulated balance of cell proliferation and cell death and ultimately evolving into a population of cells that can invade tissues and metastasize to distant sites, causing significant morbidity and, if untreated, death of the host (5). When cancer arises cancer cells are no longer regulated by the normal control mechanisms, the bioelectric signals inside and between cancer cells also become abnormal. Merrill Garnett has reported that all cancer cells have abnormal electron transfer systems while normal cell development involves normal energy flows (6).

The Historic Perspective of Discovering the Abnormal Electrical Properties of Cancer Cells

Two distinguishing biological characteristics of malignant tumors are their ability to invade adjacent normal tissues and their ability to produce secondary tumors in distant parts of the body (7). There is evidence to indicate that the cells of normal tissues and also the cells of benign tumors are so firmly attached to one another that they are unable to escape. In contrast, the cells of malignant tumors are often found in the body free from the parent tumor (7). The reason that the cancer cells become free movement is considered as their greatly reduced adhesiveness.

Back to 1940s, Coman and colleagues (8-10) seem the pioneer researches to observe changes in the mutual adhesiveness properties of tumorous cells. While he was making attempts to separate single cancer cells from each other, Coman noticed something peculiar about cancer cells: they were much easier to be separated from each other than their normal cell counterparts with micromanipulator. When the forces of the separating needle to pull apart two cells were measured and compared, the average forces to pull apart cancer cells were 3 times smaller than that needed for separating normal cells. He initially noticed this phenomenon in the carcinomas from the lip. Then similar observations were made in cervical squamous cell carcinomas and glandular adenocarcinomas (11). It was theorized at that time that such a cellular behavior might be responsible for cancer cells to break free from original tumor and metastasize to distant sites. Later on, Abercrombie and Heaysman also noticed that, when cultured on culture plates, the growth of normal cells stopped if the cells began to touch each other, a phenomenon termed as contact inhibition. As result, normal cells could only grow as a monolayer. However, sarcoma cells seemed to have lost such a contact inhibition and grew on top of each other as three-dimensional aggregates (12, 13). It was thought that loss of contact inhibition was also due to a loss of cell adhesion, and cancer cells obtained some forces to propel themselves from each other (14). After that it was reasoned that the strong adhesiveness could only be achieved among similar cells with minimal amount of surface charges. A loss of cell adhesion could only suggest that cancer cells might have gained excess surface charges (15, 16). This excess charge results in a greater electrostatic repulsive force between cells and disrupts the attractive force of contacting membranes that is caused by other reactions (17). In 1950's, in order to test the theory that cancerous cells might have gained surface charges, Ambrose et al. used cell electrophoresis technique to evaluate the cancer cells (18). They noticed that in comparison to normal cells with no movement or with slight movement towards the anode, cancer cells were indeed moving towards the anode, indicating that they are negatively charged on their surface. This might be the first demonstration for the negative charges on the cancer cells. This observation was also extended into several other cancer lines from kidneys and livers and as well as fresh primary cancer cells (19-21). All the above investigations give evidence that the lessened mutual adhesiveness is characteristic of carcinoma cells generally, and the reduction in cohesive strength between carcinoma cells might be attributed to a considerably excess negative electrical charge on membrane surfaces than the homologous normal cells that reflect structural-functional changes.

In later years, Ambrose et al. expand the studies with additional techniques to detect the surface charges of cancer cells (22). In that research, on examination of the cells microscopically 90 seconds after mixing with polyethylene imine (PEI) at very low concentrations, Ehrlich ascites cells were found to be almost completely agglutinated into clumps of varying size. Some aggregates contained up to 50 cells. In the control samples of untreated cells, groups from two to four cells in contact were observed, but no group of larger size could be seen. Comparison has been made with red blood cells and spleen cells. By mixing the PEI with the red blood cells, these cells did not clump or form rouleaux even up to 3 hours after mounting and showed a normal appearance. PEI agglutinated the tumor cells selectively, having less affinity both for red blood cells and spleen cells. It was reported that erythrocytes carry a high negative surface charge

like tumor cells, but these results suggest that, at least in this transplanted tumor, the distribution of charges on the cell surface differs from that of the erythrocytes. A similar agglutinating effect was observed with another positively charged polyelectrolyte, polyvinyl pyridinium bromide. However, when the experiment was carried out using polyglutamic acid or heparin, two typical negatively charged polyelectrolytes, no agglutination was observed in cell suspensions. Also, there was no visible change occurred when the cells were incubated with the nonelectrolyte polymer, polysarcosine. Besides, the positively charged polyelectrolytes also displayed remarkable antitumor activity in vivo when administered intraperitoneally (i.p.) to treat 1-day intraperitoneal Ehrlich ascites. Therefore, binding to positively charged polymers suggested once again that there was a strong negative charge on the surface of cancer cells but not on normal cells.

In addition to the aggregation effect, the anticancer effects of several positively charged materials were also tested. Polycations like polyethyleneimine, polyvinylamine, polypropyleneimine, polylysine and diethylaminoethyl-Dextran, positively charged colloidal ferric oxide particles and cationized ferritin all showed significant anticancer effects in both cultured cells and modeled cancer animals (23-30).

The Reason of the Enhanced Surface Negative Charge of Cancer Cells

The popular speculations about the cause of obviously more negative surface charge on cancer cells than that of normal cells is the significant gain of anionic moieties on the outside of cancer cell plasma membrane, such as the sialic acid moiety of immobile glycolipids and glycoprotein or the serine head group of phosphatidylserine of the lipid bilayer (31-36). Forrester et al. (33) demonstrated that sialic acid anions are responsible for a major portion of the surface negative charges on erythrocytes and various tumor cells. Analyses of several types of human cancer tissues revealed that the area of malignancy contained almost twice as much sialic acid as the normal areas of the same tissues (34). BMAP-27 and BMAP-28, cationic host defense peptides from the cathelicidin family, exhibited lower activity on cancer cells when sialic acid had been cleaved off (36), which suggested that sialic acid contributes to the net negative charge on the cell membrane and the outside negative charge seems to act as an initial interaction site for the peptides.

However, such proposition about the overexpression of sialic acid moiety and phosphatidylserine on the surface of cancer cells are still controversial. First, exposure of the negatively charged phosphatidylserine on the cell surface mainly results from the loss of asymmetry occurs not only during malignant transformation, but also at the time of cell injury, apoptosis, necrosis and cell activation (37-39). There is also an increase in sialic acid-rich glycoproteins in inflammatory diseases (40, 41). There have not been consistent results showing that much more phosphatidylserine or sialic acid on the surface of cancer cells than normal cells. Second, some reports showed that enzymatic removal of sialic acids from the outer membrane of cancer cells could not affect the electrophoretic mobility of cancer cells (42-45), suggesting the immobile anionic groups contribute very little to the cellular surface charges. Third, in comparison to the massive amount of mobile ions that are known to be responsible for the electrical properties of surface membranes, the number of immobile ionic groups is just too small to be useful. The research field of bioelectricity in cells has been at difficult cross-points of biology, physics, and chemistry. Because of the lack of tools for such measurement in mammalian cells, the research for cancer cellular electricity has been plagued with much less understanding than other signaling mechanisms for cells.

Applications Based On the Unique Surface Charge Property of Cancer Cells

Although it is still difficult to fully understand the unique charge property of the cancer cell, the negatively charged cancer cell surface has been paid much attention to for several decades, especially in the application of cationic polymers or polycation functionalized nanomaterials as the targeted anti-cancer drug carriers in drug delivery system.

Polylysine

Polylysine (ε-poly-L-lysine, EPL), which belongs to the group of cationic polymers, is typically produced as a homo-polypeptide of approximately 25-30 L-lysine residues. Polylysine showed unique antimicrobial activity against yeast, fungi, Gram-positive and -negative bacteria at a low concentration while have no cytotoxicity effect on healthy eukaryotes even at a high concentration (46). The proposed antimicrobial mechanism is that cationic polylysine are able to absorb electrostatically to negatively charged cell surfaces of microorganisms, followed by a stripping of the outer membrane, then abnormal distribution of the cytoplasm, and finally cell death (47).

By incubation of the tumor cells with polylysine or lysine-rich histone fractions, Shah et al. observed the obviously inhibitory effect on the growth of transplantable mouse mammary tumors (48). The investigation about the effects of polylysine on the electrophoretic mobility (zeta potential) of saline-washed Ehrlich ascites tumor cells have shown that the polylysine change the net negative charge of the tumor cell membrane to zero or high positive values (27). It could be reasonably suggested that the negative surface charge of the tumor cells play an important role in its highly invasive properties and the inhibition effect of

polylysine to the growth of tumor. Afterwards, Arnold et al. (49) have discovered that White Swiss mice show nearly a 100% remission from subsequent tumor growth when given optimal doses of polylysine i.p. after inoculating with Ehrlich ascites cells. The vitro cell viability study indicates that polylysine has a high affinity and a marked concentration dependent cytotoxicity for Hela cells (49). Studies with a fluorescent polylysine derivative also demonstrated that the largest amount of polylysine derivative binds to the lipoprotein surface of Ehrlich ascites tumor cells and very little penetrate the cell membrane to enter the tumor cells (50). More recently, a cationic polylysine dendrimer have been shown to have intrinsic antiangiogenic activity in vitro and in vivo assays (51). Intravenous administration of polylysine dendrimer resulted in persistently accumulation in tumor sites, reduction in vascularization, extensive apoptosis/necrosis within the tumor tissue, without any remarkable histological or physiological abnormality in non-tumor tissues such as liver and kidneys (51). Later on, a complexation of doxorubicin (DOX) with cationic poly-L-lysine dendrimer have been developed and shown significant increase in DOX penetration and the toxicity of the drug upon complexation both in multicellular tumor spheroids (MTS), and in vivo solid tumors (52). These evidences clearly show the cationic polylysine and some theirs derivative/drug complexes are capable of bonding and producing a selective toxicity to some tumor cells and tissue mainly due to the electrostatic interaction. Such results give the potential of cationic polylysine dendrimer-drug complexes as synergistic antiangiogenic/anticancer therapeutics to be translated clinically.

Cationic Liposomes

Cationic liposomes, first described in the laboratory of Alec Bangham for the purpose of studying membrane diffusion (53), have been used for a variety of delivery systems for cancer and other disorders (54). In comparison to other gene delivery modes, such as viral vectors, cationic liposomes have significant advantages in terms of simple to synthesis, more biologically safety, and the ability of tailoring for specific applications (55).

Tumor angiogenesis is a formation of neovessels from preexisting vessels in solid tumors, which is a consistent feature of tumors and critical for the support of tumor growth and progression, not only by providing nutrients, oxygen, growth factors and other substances to tumor cells, but also by allowing metastatic cells into circulation (56). It has been proven that the angiogenic tumor vasculature also carries large more amounts of negative charge than peripheral normal tissue (57). Many studies have been developed to investigate the quite selective targeting of cationic liposomes as carrier system for delivering anticancer agents to angiogenic tumor vasculature and tumor cells. It has been shown by Thurston et al. (58) that angiogenic blood vessels in tumors bound and took up cationic liposomes much more than the corresponding normal vessels. Confocal microscopic measurements showed that angiogenic endothelial cells in tumors more bound and uptake fluorescently labeled cationic liposomes with average 15-33 times than corresponding normal endothelial cells. Angiogenic endothelial cells in the model of angiogenesis also selectively took up DNA at cationic liposome complexes, but not anionic, neutral, or sterically stabilized neutral liposomes (58). Further research by Krasnici et al. (57) demonstrated that cationic liposomes but not anionic or neutral liposomes preferentially accumulated in the A-Mel-3 melanoma tissue and tumor vasculature of hamster up to 3-fold compare with normal surrounding host tissue when administered intravenously. The preferential uptake of cationic liposomes in the solid tumor was mainly caused by a highly selective accumulation of liposomes within angiogenic tumor microvessels, whereas neutral and anionic liposomes extravasated unspecifically into the parenchyma several minutes after intravenous injection. Similarly, Nomura et al. (59) reported that clearance of positively charged liposomes was greatly retarded in contrast to neutral liposomes, which immediately appeared in the venous outflow perfusate following intratumoral injection. The preferential and prolonged accumulation in angiogenic tumor vessels seems to be a general feature of cationic liposomes, independent of a certain tumor type. Campbell et al. compared the biodistribution of negatively charged liposomes (−20 mV) and positively charged liposomes (+31 mV) after intravenous injection into tumor-bearing mice (60). While liver was the major destination for both formulations, positively charged liposomes showed higher association with tumor blood vessels than negatively charged ones. Further investigation showed that an increase in cationic lipid from 10 to 50 mol% in PEG-coated cationic liposomes led to a 2-fold increase in liposomal accumulation in tumor vessels, suggesting cationic charge determine the distribution of liposomes between the vascular and extravascular compartments of tissue (60). Recently, using a tumor-bearing mouse model, Abu Lila et al. (61) emphasized that PEG-coated cationic liposomes showed 2-3-fold higher accumulation in tumor tissue than PEG-coated neutral liposomes. This enhanced intra-tumor accumulation was ascribed to the selective binding of PEG-coated cationic liposomes, not only to tumor angiogenic vessels, but to tumor cells as well. Schmitt-Sody et al. (62) demonstrate that cationic liposomes maintain their ability to selectively accumulate tumor vasculature and tumor tissue as compared with surrounding normal tissue after encapsulation of the cytotoxic drug paclitaxel. Moreover, the tumor growth revealed a remarkable retardation after treatment with paclitaxel encapsulated in cationic liposomes in comparison with any other groups, which demonstrated that treatment

with this liposomal formulation significantly increased the antitumor efficacy of the cytotoxic drug paclitaxel. Similarly, Kunstfeld et al. (63) also demonstrated that paclitaxel encapsulated in cationic liposomes diminishes tumor angiogenesis and inhibits melanoma growth in SCID mice. In contrast, paclitaxel administered in its normal Cremophor EL medium, while showing an inhibitory effect in cell culture, was unable to significantly decrease angiogenesis and tumour growth in vivo.

As described above, the promising characteristics of cationic liposomes as carrier system for the delivery of anticancer agents to tumor cells and tumor microenvironment are strongly takes advantage of the natural affinity of cationic surface of those carrier systems for anionic sites in the tumor microvasculature and the surface of tumor cells. Many liposomal drugs have approved for cancer therapy notably Doxil for doxorubicin (Johnson & Johnson, New Brunswick, USA), Lipusu for paclitaxel (Luye Pharma Group, Yantai, China), and Marqibo for vincristine (Talon Therapeutics, South San Francisco, USA) (64, 65). Cationic liposomes have been showing promising development prospects in oncology clinical pharmacology and therapeutics.

Host Defense Peptides

Natural antimicrobial peptides (AMPs), also referred to host defense peptides (HDPs) as a more generic term, constitute a major component of the ancient, nonspecific innate defense system in a variety of multicellular organisms. They were initially discovered because of their antimicrobial activity (66, 67). Despite the diversity in their amino acid sequences and secondary structures, HDPs share many common features, including amphipathic, small size (generally 12-50 amino acids), have an overall net positive charge and have a high content of cationic and hydrophobic residues (67, 68). HDPs have a very high affinity with negatively charged microorganism membranes. They also have a strong tendency to form polymers with a staved-barrel shape. The positively charged portions face the center and form a water channel. The hydrophobic portions fuse with the lipid bilayers. Thus the cationic peptides form water-permeable pore on the plasma membrane of target cells (67). Interestingly, a large number of HDPs not only have the ability to kill both Gram-positive and Gram-negative bacteria, but also exhibit a broad spectrum of cytotoxic activity against cancer cells (67). Some of these peptides have been found to have lipopolysaccharide (LPS) neutralizing ability and the capacity to recruit the adaptive immune response (69). While not all HDPs are able to kill cancer cells, recently, the antimicrobial peptide database lists more than 100 natural host defense peptides with antitumor activity (70). Unlike conventional chemotherapeutic agents which exert a systemic effect and typically target the rapidly dividing cancer cells is often associated with toxicity side-effects caused by inadvertent drug-induced damage to healthy cells and tissues, most of these cationic HDPs have been found to target the membrane of cancer cells, leading to cell lysis and death, which followed the similar mechanism of anti-bacteria. Thus, HDPs offer the possibility of a new family of therapeutic agents, which are different with or complementary to existing chemotherapeutic agents and have shown the ability to bypass the multidrug-resistance mechanism (71). Due to the altered metabolic abnormalities of malignant cells, fundamental differences exist between the cell membranes of malignant cells and normal cells. These differences likely account for the ability of certain HDPs to kill cancer cells specificity while have less effect of healthy cells. In this regard, electrostatic interactions between cationic HDPs and anionic cell membrane components are believed to be a major factor in the selective killing of cancer cells by HDPs.

Magainins 1 and magainins 2, originally isolated from African clawed frog Xenopus laevis skin, exhibited in vitro the antibiotic activity on both Gram-positive and Gram-negative strains of bacteria, fungi, and protozoa (72, 73). It was suggested that these peptides act on the phospholipid of the plasma membrane to perform antimicrobial activity (74). In 1990, Cruciani et al. (75) reported that magainins and synthetic analogues can rapidly and specifically lyse hematopoietic tumor and solid tumor cells with a relative cytotoxic potency that parallels their antibacterial efficiency and at concentrations that are relatively nontoxic to well-differentiated cells. Magainin G showed the most selectivity cytotoxic for tumor cells, which have virtually no cytolytic effect on peripheral blood lymphocytes (PBLs) and polymorphonuclear neutrophils (PMNs) after 60 min of incubation at a concentration twice of that required to lyse 100% of tumor cells in 10 min (75). Ohsaki et al. (76) have investigated the antitumor activity of Synthetic magainin A and magainin G against six small cell lung cancer (SCLC) cell lines. The results suggested that magainin A and magainin G showed consistent growth inhibition against all six SCLC cell lines. Meanwhile, these peptides were less effective against normal human fibroblast cells than malignant cells. In vivo efficiency research against murine ascites tumors has shown that Magainin 2 and two more analogues had activity against P388 leukemia, S180 ascites, and a spontaneous ovarian tumor by increasing in life span of over 100% when injected i.p.. The antitumor activity was suggested to be related to short duration non-receptor-driven contact with target cell membranes (77). Papo et al. (78) have reported that a new series of cationic diastereomeric peptides are highly toxic and selective toward cancer cells compared to normal cells. It was suggested that the cell selectivity was predominantly determined by improved electrostatic attraction of the peptides to an increase in the level of large amount of acidic components on the surface of cancer cells, but may

not by the slight increase in the level of PS in the outer surface of the cancer cell membranes (78). Another similar peptide, a 15-amino acids diastereomer composed of D - and L - leucines, arginines, and lysines, was shown to act against the mouse melanoma and lung carcinoma cell lines and to significantly inhibit lung metastasis in mice with no detectable side effects (79). An intratumorally injection of a 15-mer all L-amino acids lytic peptide and its diastereomer completely inhibited the growth of both androgen-dependent and androgen-independent human prostate carcinomas without affecting the nonmalignant neighboring cells (80). A necrotic mechanism of killing rather than an apoptotic was suggested, which involves four major steps in the following process: (a) amphipathic-D binds initially to distinct sites on the negatively charged cytoplasmic membrane, which is governed mainly by electrostatic interactions, and then it reaches a threshold concentration; (b) Membrane binding forces the peptide to adopt a functional structure, which allows the peptide induces marked membrane depolarization; (c) the kinetics of membrane permeation is fast followed by an equal distribution of the peptide in the cytoplasm; and (d) the cells become necrotic (80). This electrostatic interaction induced cancer necrocytosis model was recognized as the typical cancer killing mechanism of cationic HDPs (71, 81, 82). Certainly, besides of the electrostatic interaction of HDPs with the surface of cancer cells, a great deal of further study must be devoted to studying the structure, dynamics, topology of the activated HDPs and which of the characteristics of a cancer cell make some HDPs preferentially target them.

Moreover, in human body, non-immune cells usually synthesize cationic peptides at low levels. Therefore their defensive abilities are much lower than that of innate immune system. In contrast, granulocytes can produce cationic human neutrophil peptides (HNPs) at extremely high level of 10 mg/ml. This ability would make granulocytes the most effective immune cells to kill cells with negative charges on their surfaces. Recently, Z. Cui et al. reported a serendipitous discovery of a cancer complete resistant/ spontaneous regression (CR/SR) "super-mice" family (83), in which it showed that the cancer resistance in SR/CR mice was mediated by the special immune system, exactly the innate immune system with neutrophils act as the main effective attacking cells (84, 85). In a similar way as the antimicrobial action of HDPs, the cancer killing process of neutrophils from SR/CR mice were investigated and showed by three phases: infiltration, tight contact and tumor destruction (85, 86). Although the exactly mechanism at gene level of this unique recognition reaction have not been clarified, the cationic peptides releasing from neutrophils and the unique surface negative charge property of cancer cells are considered as the main factors of cancer cell targeting and destruction mechanisms (87, 88).

DEAE-Dextran

Diethylaminoethyl-Dextran (DEAE-Dextran), as a polycatonic derivative of Dextran, has been used in many applications in molecular biology and the health-care sector, such as in DNA transfection (89), gene therapy (90), and enhancer of viral infectivity (91). The effect of different DEAE-dextran derivatives varied in molecular weight and charge density (degree of substitution with diethyl-amino-ethyl groups) on the surface charge of tumor cells has been investigated by Thorling et al. (92) It was shown that the higher molecular weight and higher degree of substitution gave a stronger binding to the tumor cell surface and the ability to neutralize the negative charge of the cell surface (92). In addition, it has been shown in the *in vivo* experiment results that the most effective inhibitory effect on the growth of transplanted tumor was obtained by the highest degree of positive charge density in DEAE dextran, which seems that the effect of the compounds on the negative electric charge of tumor cell surface is essential for the inhibitory effect observed in these experiments. It is worthwhile to note that cells previously treated with neuraminidase and subsequently incubated with labeled DEAE dextran would also bind the DEAE dextran. It is supposed in these instances that the DEAE dextran is bound to other acid groups on the cell surface which have been exposed after removal of the sialic acid component of the mucoprotein layer (92).

Summary

Bioelectricity is the sign of life. Cellular electricity is present in every life form and in every living cell. It plays essential roles in intercellular and intracellular communication, energy production and many designated cellular functions. Cancer cells are a class of pathological cells with profoundly altered energy metabolism and cross-membrane flow of ions. From 1940s, the phenomenon that cancer cells gain abnormal surface electrical charges has been discovered and investigated via different tools, such as micromanipulator, microscopy, cell electrophoresis, polyelectrolyte and positively charged nanomaterials assisted pathomorphology studies. Due to the lack of an effective tool for the real-time measurement of electrical properties of individual live intact cells, it still has not been understood well about the cancer cellular electricity mechanisms. In other words, the unique surface charge property of cancer cells and the interchange of cellular electricity does not seem to get enough attendance although enormous efforts has been paid for cancer research as a general research field. In this article, we give a historic perspective review about the discovering, investigating and application of the abnormal surface electrical properties of cancer cells. Although it is still difficult to fully understand the unique properties of cancer cells. We reasonably propose that the significantly enhanced surface negative charge of cancer cells may be a neglected hall-

mark of cancer which cannot be overstated. Perhaps, with the onset of innovative technologies, the surface electrical properties of cancer cells can attract sufficient efforts to further understand their mechanisms and implications in the therapeutic and diagnostic purposes of cancer.■

Conflict of Interests

None

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


Love the Wave
Love the Earth

How Long Would It Take for Humans to Get to the Closest Star from Our Sun?

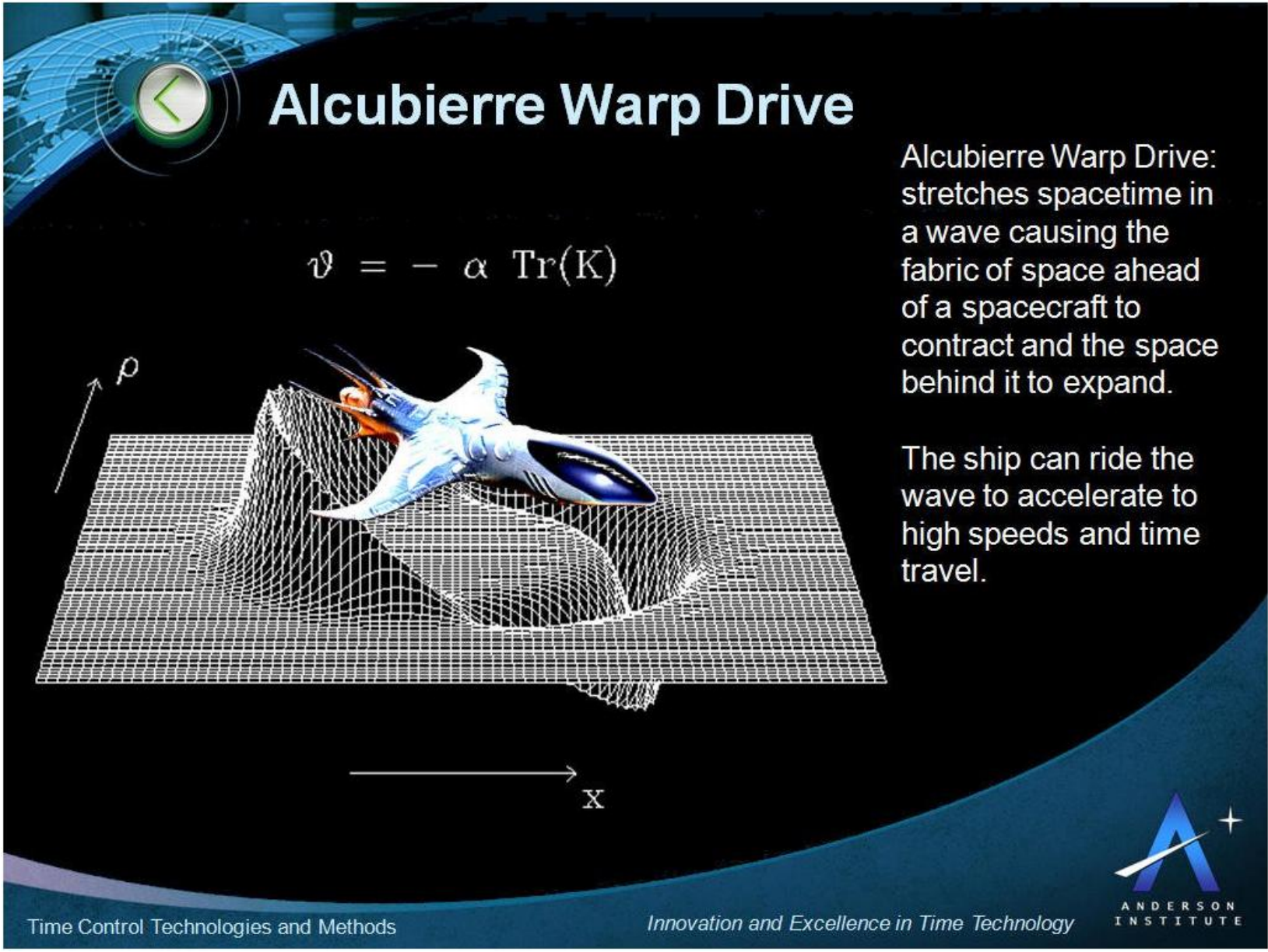
THAT IS why NASA has no plans at present to send a spacecraft to any of the 1,876 known planets (as of January 9, 2015) beyond our solar system.

Alpha Centauri is the nearest star system to our sun at 4.3 light-years away. Can't we even go that far? The answer is not easily. A distance of 4.3 light-years equals *trillions* of miles away from Earth – nearly 300,000 times the distance from the Earth to the sun. How might we travel to Alpha Centauri, the next-nearest star? And how long would it take to get there?

Would A Conventional Rocket Work?

Consider the Space Shuttle, which traveled only a few hundred kilometers into space. If Earth were the size of a sand grain, this would be about the width of a hair in contrast to a 10-kilometer distance to Alpha Centauri. You'd need about 10,000 shuttle main engines in sequence just to build up a decent speed (say, 1/100th light speed). The Space Shuttles weren't starships. At a maximum speed of about 17,600 mph (about 28,300 kph), it would have taken a

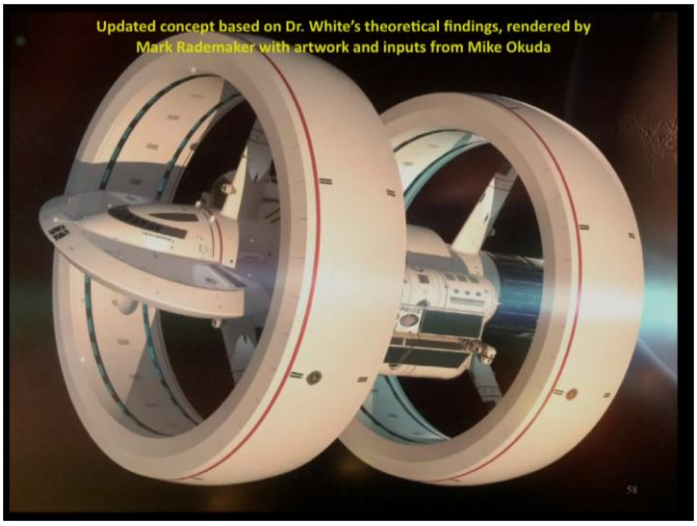
Space Shuttle about 165,000 years to reach Alpha Centauri. These can get us to space, but won't take us to the stars. How about the Voyager spacecraft? These two unmanned space probes – Voyager 1 and Voyager 2 – were launched in 1977. They're now heading out of our solar system. The Voyagers aren't aimed toward Alpha Centauri, but if they were, they'd take tens of thousands of years to get there. On the other hand, eventually, the Voyagers will pass other stars. In about 40,000 years, Voyager 1 will drift within 1.6 light-years (9.3 trillion miles) of AC+79 3888, a star in the constellation of Camelopardalis. In some 296,000 years, Voyager 2 will pass 4.3 light-years from Sirius, the



brightest star in the sky. Hmm, 4.3 light-years. That's the distance between us and Alpha Centauri. The problem with conventional rockets is that, if you're carrying fuel, you need *more fuel in order to carry your fuel* to accomplish star-to-star travel.

Warp drive?

Using current technology, a trip to Alpha Centauri would take tens to hundreds of thousands of years. But what if we would travel *faster than light*? Sound impossible? A couple of years ago, Dr. Harold "Sonny" White – who leads NASA's Advanced Propulsion Team at Johnson Space Center – claimed to have made a discovery which made plausible the idea of faster-than-light travel, via a concept known as the Alcubierre warp drive. This concept is based on ideas put forward by Mexican physicist Miguel Alcubierre in 1994. He suggested that faster-than-light travel might be achieved by *distorting spacetime*, as shown in the illustration above. Harold "Sonny" White has been working to investigate these ideas further, and, in June of 2014, he unveiled images of what a faster-than-light ship might look like. Artist Mark Rademaker based these designs on White's theoretical ideas. He said creating them took more than 1,600 hours, and they *are* very cool. The video below presents Harold White's talk at the SpaceVision 2013 Space Conference in November, 2013 in Phoenix. He talks about the concepts and progress in warp-drive development over recent decades. Is it faster-than-light travel possible, via the Alcubierre warp drive? As with conventional propulsion systems, the problem is energy. In this case, it's the type of energy the warp drive



would need. Daily Kos said: In order to form the warp field/bubble, a region of space-time with negative energy density (i.e. repulsing space-time) is necessary. Scientific models predict exotic matter with a negative energy may exist, but it has never been observed. All forms of matter and light have a positive energy density, and create an attractive gravitational field. So faster-than-light travel via the Alcubierre warp drive is highly speculative, to say the least. With current technologies, it's not possible. What a spaceship with warp drive might look like. However, if it could be accomplished, it would reduce the travel time to Alpha Centauri from thousands of years to *just days*.

Other alternate propulsion methods have been discussed, for example, antimatter engines. They work on the principle that, when antimatter and matter meet, they annihilate each other, releasing vast amounts of energy.

Scientists have observed bits of antimatter in particle accelerators. But no one knows how to create enough antimatter, or how to store it, for a trip to the stars. How about light sails? This very romantic notion for travel among the stars would rely on thin, lightweight reflective sails, powered by the sun, other stars, or even lasers fired from Earth. You start slow, but accelerate up to light speeds. However, no one imagines a light sail could enable us to travel to Alpha Centauri within a human lifetime. But the propulsion issues are just part of the problem. The real problem might be *when to decide to go*.

The Real Problem with Traveling to Alpha Centauri

Let's suppose that faster-than-light travel isn't going to become a reality. Suppose we have to chose another method of travel – a conventionally powered space arc of some kind, or even an antimatter drive, or a solar sail. Now suppose we set out for a trip among the stars. Suppose that, generations from now, our descendants arrive at a planet in the Alpha Centauri system. They might be greeted by brass bands and crowds of earthlings – who left later, but traveled via a more efficient process – and so made the trip in a shorter time. All aboard! Bottom line: At 4.3 light-years away, the Alpha Centauri system is the nearest star system to our Earth and sun, but getting there would be extremely difficult.■


Working like a worker bee?
Relax yourself.....

AUTHOR GUIDE

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