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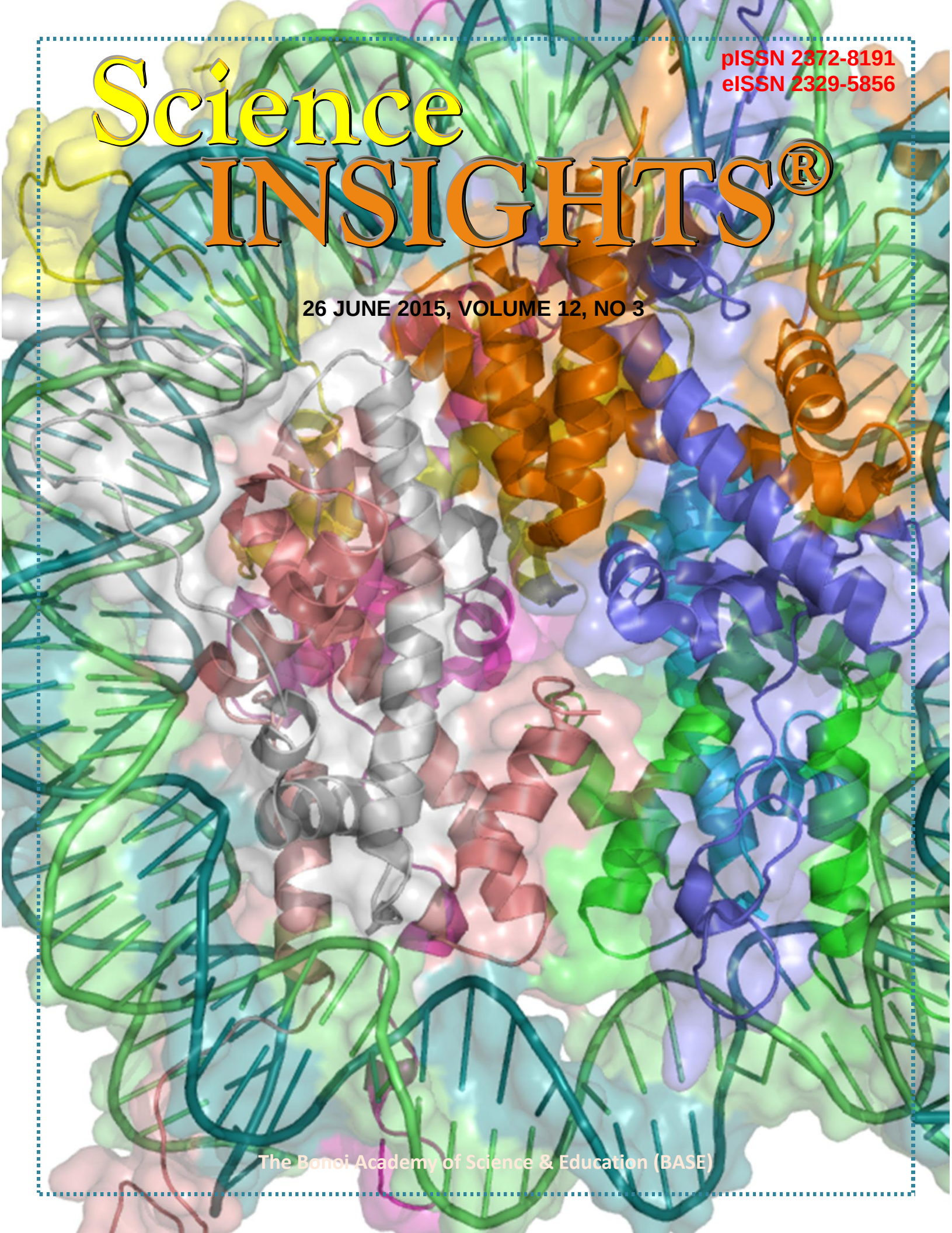

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EDITORS (Alphabetically)

Editorial Office

Monica R. **Silber** (*Editor Assistant*): monica.silber@bonoi.org
Susan J. **Song** (*Secretary*): susan.song@bonoi.org
Amie S. **Cahill** (*Technician*): amie.cahill@bonoi.org
Editorial Office: editorial-office@bonoi.org

Founding-Committee of the BASE

Regional Office

CHINA (Mainland)

Contact Info: **Haibo (Herbert) Wu**, No.123, Tianfeixiang, Nanjing 210004, Jiangsu, China

Tel: +86-25-150 6228 2214

Email: herbert.wu@bonoi.org

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NEWS

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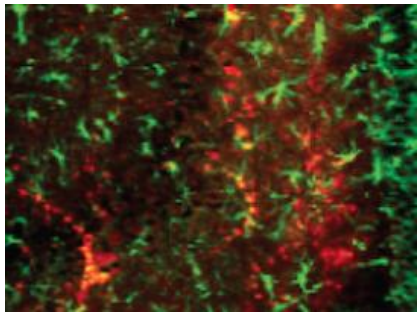
COMMON SCIENCE



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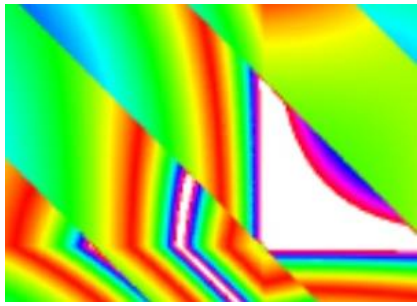

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COVER

Pain itself forms an overbalanced microenvironment in which people undertakes individualized changes in its neurobiological, psychological, endocrinological and genetic properties especially in the context of chronic pain or when the acute pain transmitted to chronicity. See page 429.

Image: BASE illustrating group

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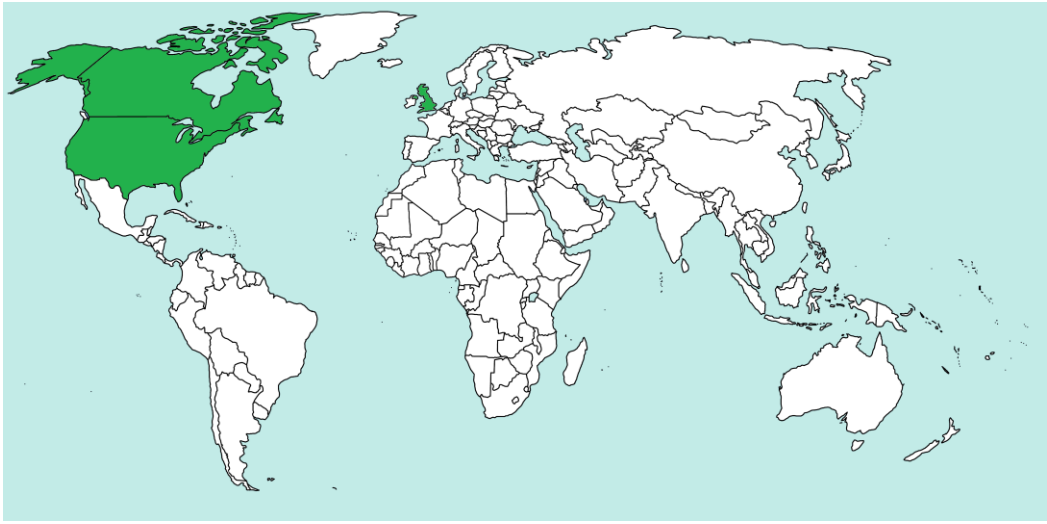
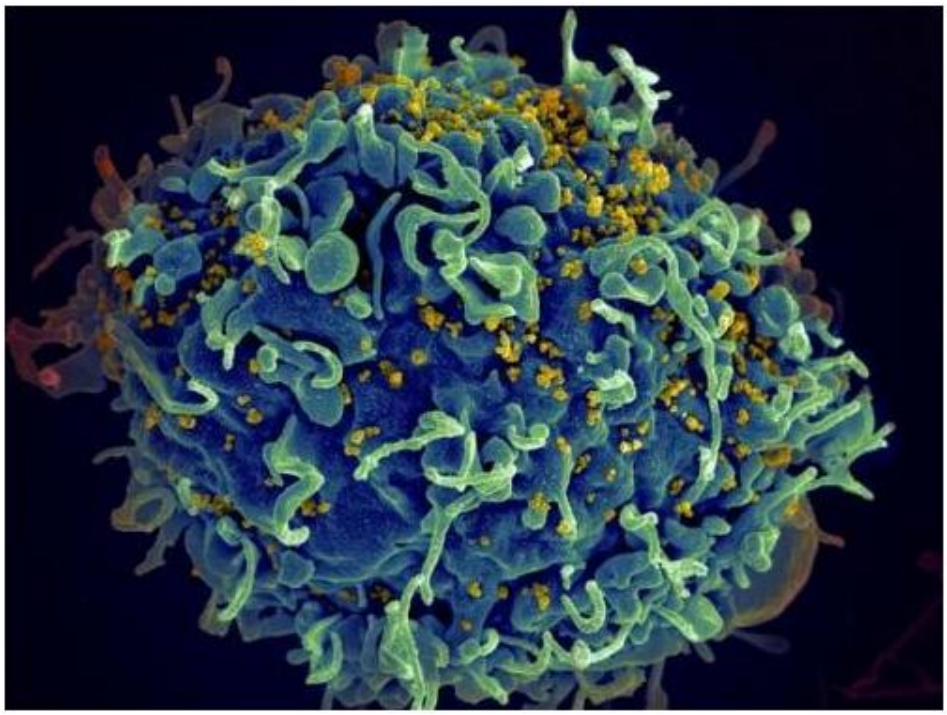
Stanford, USA

Limited Mutations Involved In Transmission of Drug-Resistant HIV



In the largest study of its kind to date, researchers at Stanford University School of Medicine and their colleagues have found that worldwide only a limited number of mutations are responsible for most cases of transmission of drug-resistant HIV. HIV, the virus that causes AIDS, can mutate in the presence of antiviral drugs, and these mutations can be transmitted from one person to the next. In the new study of more than 50,000 patients in 111 countries, the researchers found a small group of mutations accounted for a majority of the cases of transmission-related resistance to the HIV drugs used to treat infections in resource-limited settings. The results suggest the levels of transmission of drug-resistant strains have not increased globally as much as once feared, said Robert Shafer, professor of medicine at Stanford and principal investigator for the study. "What we are showing is that the rates of transmitted drug-resistant HIV in the low- and middle-income countries most affected by HIV have increased modestly. The rate of increase in sub-Saharan Africa has been low, and an increase has not been detected in south Asia and Southeast Asia. That's good news," Shafer said. However, there continues to be an increase in drug resistance because the regimens used by HIV patients in lower-income countries are often not as robust as those used in upper-income countries, and strict adherence to a daily, lifetime regimen of taking the pills is challenging, particularly for people in the poorest parts of the world, he noted. "It is inevitable that transmitted drug resistance will increase further, so we need to continue ongoing monitoring to ensure successful, long-term treatment outcomes for the millions of people on therapy worldwide," Shafer said. He said the findings could have important implications for treatment in these hard-hit regions, leading to the possible development of an inexpensive test for key mutations to help determine which drugs should be given to previously untreated patients.

Since 2003, the international community has made major strides toward the goal of universal antiretroviral treatment for HIV, with 11.7 million people in low- and middle-income countries now receiving the lifesaving therapy, according to the Joint United Nations Programme on HIV/AIDS. But there has been concern that, with wider availability of these medications, drug resistance could spread and rapidly reverse those gains. To gauge the extent of the problem, Shafer and his colleagues reviewed HIV sequencing data on 50,870 individuals across the globe, taken from 287 studies published between 2000 and 2013. Nearly 60 medical institutions on five continents contributed data for the study. The researchers analyzed each virus sequence for the presence of 93 mutations previously shown to be indicators of drug resistance. They found the overall prevalence of transmitted drug resistance ranged from 2.8 percent in sub-Saharan Africa to 11.5 percent in North America. In south Asia and Southeast Asia, the prevalence of transmitted resistance remained unchanged during the decade of expansion in drug treatment. However, many studies from sub-Saharan Africa have shown the prevalence of resistance to be more than 5 percent in recent years, Shafer noted. He said the inevitable increase in transmitted drug resistance could undermine confidence in the ability to treat HIV in low-income regions and potentially dissuade new patients from seeking care. To avoid that prospect, the study points to the possibility of creating a simple, inexpensive test for the key resistance-related mutations, which could help clinicians pinpoint the drugs likely to be most effective for individual patients. In both Africa and Asia, the researchers identified four specific resistance-related mutations that were associated with the drugs nevirapine and efavirenz. These are among an older, less-expensive class of drugs known as non-nucleoside reverse transcriptase inhibitors, typically used in the developing world as part of a standard, daily regimen. "The idea of an inexpensive test for key mutations is attractive because if it were used in conjunction with a viral load test [a measure of the amount of virus in



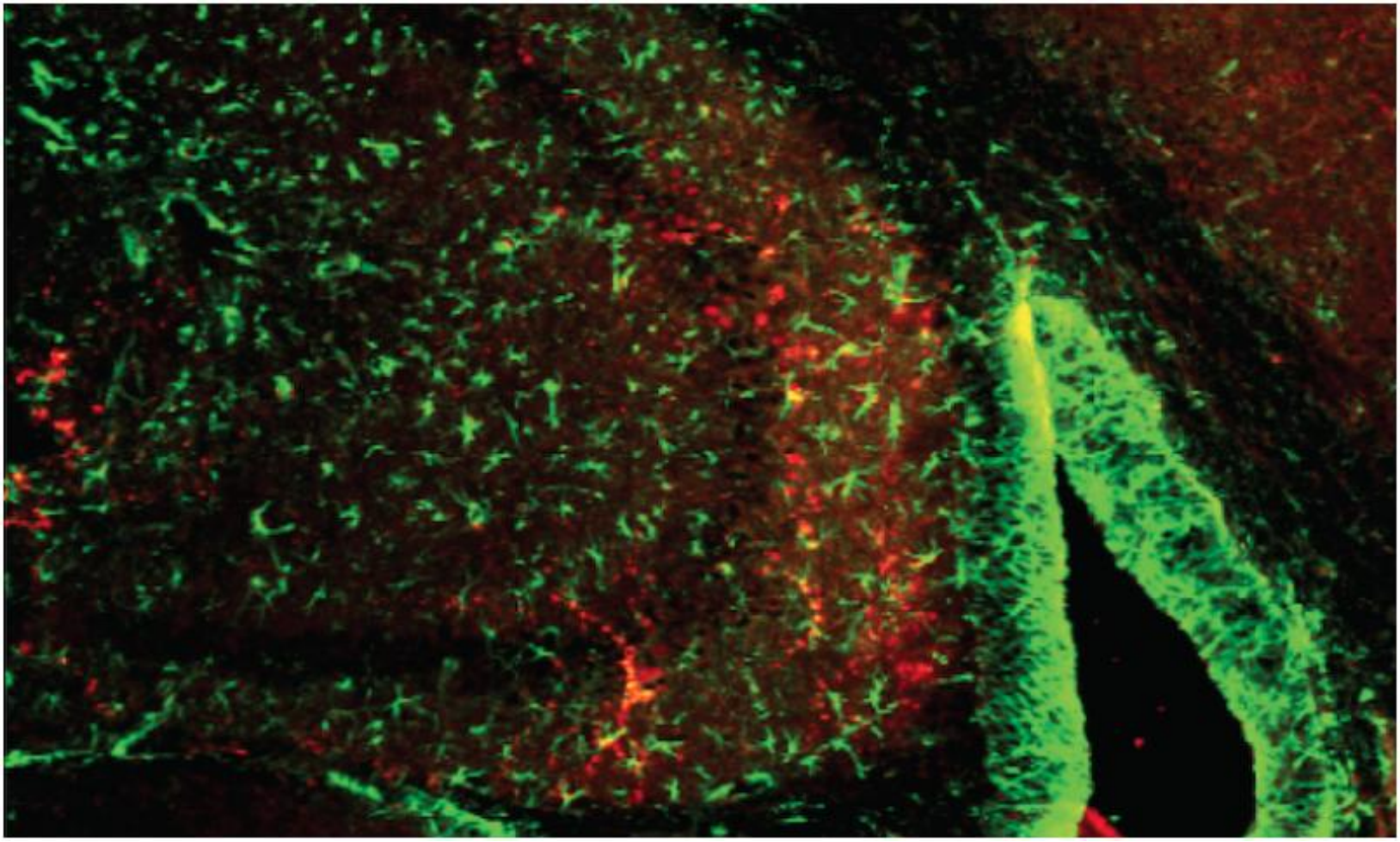
a patient's blood], it would allow physicians to know if therapy should be changed and where adherence counseling should be given," Shafer said. Patients who show signs of these mutations could be switched to newer, albeit more costly, drugs known as protease inhibitors, which are less susceptible to resistance, he said. "You could therefore shut off the flow of drug resistance by using regimens that are less vulnerable to the development of drug resistance in the first place," he said.

The study also found that the drug-resistant strains did not come from a single line of resistant viruses, but were distinctly different from each other, suggesting they had been acquired independently and not as a result of a single transmission chain. That contrasts with patterns of resistance in other microbes, such as malaria and tuberculosis, where resistant strains tend to move rapidly among populations, Shafer said. It also contrasts with an emerging pattern of drug resistance in many upper-income countries, where 20 years of HIV therapy have spawned the spread of many highly drug-resistant strains. "We are finding that the strains being detected in low-income countries are pretty much unrelated to one another. So that suggests these have not yet gained a foothold in the population, and are less often being transmitted among people who have never received the drugs before," Shafer said.

La Jolla, USA

Master Protein Enhances Learning and Memory

Just as some people seem built to run marathons and have an easier time going for miles without tiring, others are born with a knack for memorizing things, from times tables to trivia facts. These two skills — running and memorizing — are not so different as it turns out. Salk scientists and collaborators have discovered that physical and mental activities rely on a single metabolic protein that controls the flow of blood and nutrients throughout the body, as reported in the journal *Cell Metabolism*. The new study could point to potential treatments in regenerative and developmental medicine as well as ways to address defects in learning and memory. "This is all about getting energy where it's needed to 'the power plants' in the body," says Ronald Evans, director of Salk's Gene Expression Laboratory and senior author of the new paper, published April 7, 2015."The heart and muscles need a surge of energy to carry out exercise and neurons need a surge of energy to form new memories." Energy for muscles and brains, the scientists discovered, is controlled by a single protein called estrogen-related receptor gamma (ERRγ). Evans' research group has previously studied the role of ERRγ in the heart and skeletal muscles. In 2011, they discovered that promoting ERRγ activity in the muscle of sedentary mice increased blood supply to their muscles and doubled their running capacity. ERRγ, they went on to show, turns on a whole host of muscle genes that convert fat to energy. Thus, ERRγ became known as a master metabolic switch that energized muscle to enhance performance. Although studies had also shown that ERRγ was active in the brain, researchers didn't understand why — the brain burns sugar and ERRγ was previously shown to only burn fat. So the team decided to look more closely at what the protein was doing in brain cells. By first looking at isolated neurons, Liming Pei, lead and co-corresponding author of the paper, found that, as in muscle, ERRγactivates dozens of metabolic genes in brain cells. Unexpectedly, this activation related to sugar instead of fat. Neurons that lacked ERRγ could not ramp up energy production and thus had a compromised performance. "We assumed that ERRγ did the same thing throughout the body," says Evans."But we learned that it's different in the brain." ERRγ, they now conclude, turns on fat-burning pathways in muscles and sugar-burning pathways in the brain. Evans and his collaborators noticed that ERRγ in live mice was most active in the hippocampus — an area of the brain that is active in



producing new brain cells, is involved in learning and memory and is known to require lots of energy. They wondered whether ERRγ had a direct role in learning and memory. By studying mice lacking ERRγ in the brain, they found a link. While mice without the protein had normal vision, movement and balance,they were slower at learning how to swim through a water maze — and poor at remembering the maze on subsequent trials — compared to mice with normal levels of ERRγ. "What we found is that mice that missing ERRγ are basically very slow learners," says Pei. Varying levels of ERRγ could also be at the root of differences between how individual humans learn, he hypothesizes."Everyone can learn, but some people learn and memorize more efficiently than others, and we now think this could be linked to changes in brain metabolism." A better understanding of the metabolism of neurons could help point the way to improved treatments for learning and attention disorders. Andpossibly, revving up levels of ERRγ could even enhance learning, just as it enhances muscle function. "What we've shown is that memories are really built on a metabolic scaffold," says Evans. "And we think that if you want to understand learning and memory, you need to understand the circuits that underlie and power this process."

Miami, USA

Corn Husks a Promising Source of Renewable Fuel

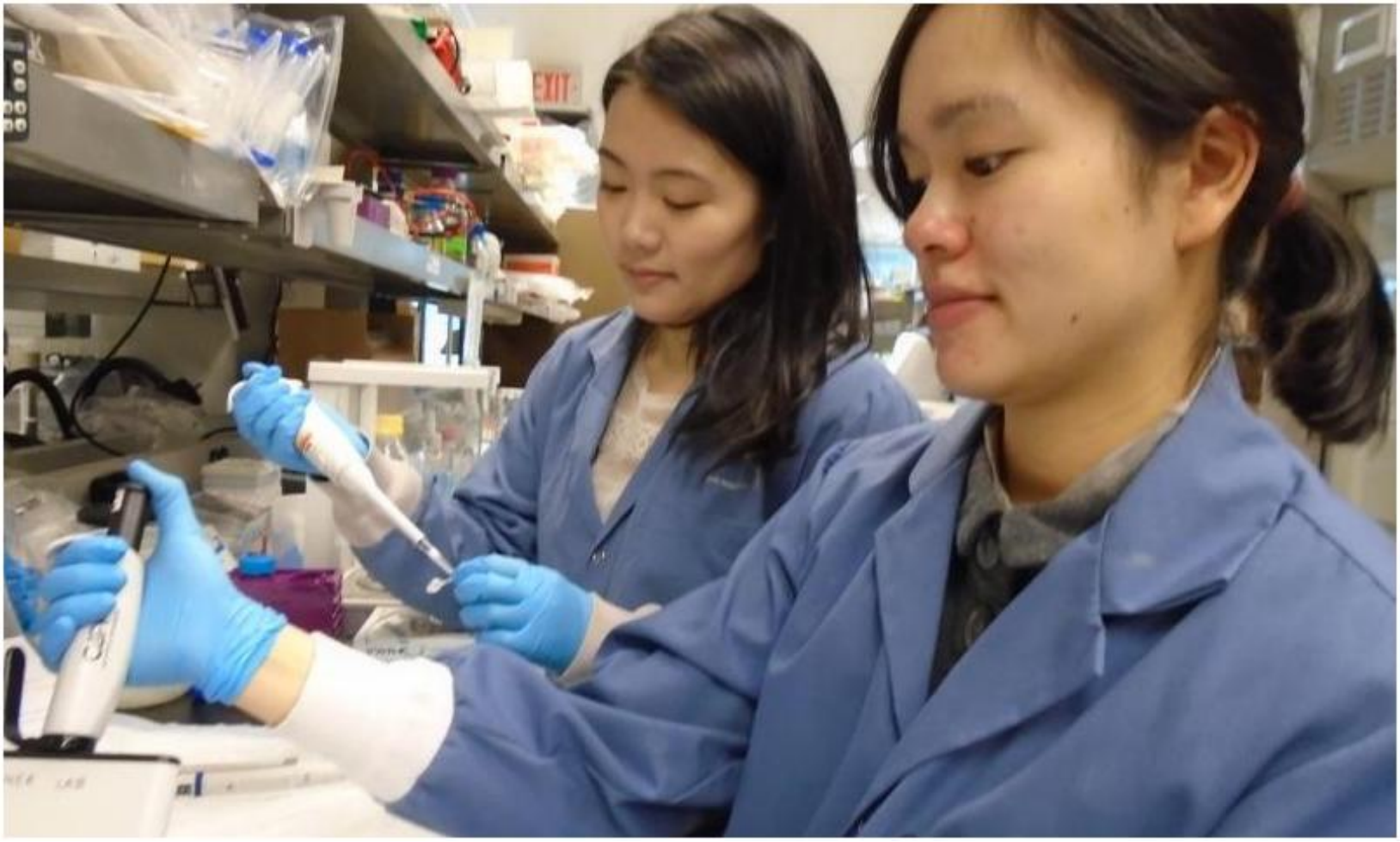
The advances by a team at Virginia Polytechnic Institute and State University save time and money while producing a zero-emissions fuel that could speed up the movement toward hydrogen-powered vehicles, said the report in the Proceedings of the National Academy of Sciences. "We have demonstrated the most important step toward a hydrogen economy -- producing distributed and affordable green hydrogen from local biomass resources," said study co-author Percival Zhang, a professor in the Department of Biological Systems Engineering at Virginia Tech. The study was led by Joe Rollin, a former doctoral student of Zhang's at Virginia Tech. Together they co-founded a start-up company called Cell-free Bioinnovations. The process builds on previous research using xylose, "the most abundant simple plant pentose sugar, to produce hydrogen yields that previously were attainable only in theory," said the PNAS report. Other hydrogen fuel production methods rely on highly processed sugars, but the Virginia Tech team used corn husks and stalks, which are known as dirty biomass, to cut costs and make the fuel easier to produce locally. Rollin found that process of breaking down corn husks and stalks into hydrogen and carbon dioxide can use both sugars glucose and xylose at the same time, not one after the other. That discovery means it is possible to speed up the rate at which hydrogen is released, while decreasing the area of the facility needed to produce it

to the size of a gas station. "We believe this exciting technology has the potential to enable the widespread use of hydrogen fuel cell vehicles around the world and displace fossil fuels," Rollin said. Experts said it is hard to know how much the new approach might cost. Funding so far has been provided by the Shell GameChanger initiative and the National Science Foundation. But Lonnie Ingram, director of the Florida Center for Renewable Chemicals and Fuels at the University of Florida, who was not involved with the study, said the work "represents a revolutionary approach that offers many new advantages. "These researchers have certainly broadened the scope of our thinking about metabolism and how it plays into the future of alternative energy production," Ingram said. Researchers say they have the necessary cash to scale up their findings to a demonstration-level, which is the next step of the project.

Toronto, CANADA

Gut Immune System Functions As a New and Effective Target in Treating Diabetes

A commonly-used drug to treat inflammatory bowel disease, such as Crohn's disease, has been shown to lower blood sugar levels in obese mice, potentially identifying the gut immune system as a new and effective target in treating diabetes in humans. "These results are novel and important because we have identified the immune system that lives in the gut as a new player in the control of blood sugar. This opens up the entire field of bowel immunology to the study of obesity and its complications such as high blood sugar," says Dan Winer, Scientist, Diabetes Research Group in the Toronto General Research Institute (TGRI), whose laboratory spearheaded this work, along with his twin brother Shawn Winer, and who are both co-senior authors on this paper. Their research is published in an article entitled, "Regulation of Obesity-Related Insulin Resistance with Gut Anti-inflammatory Agents," in the prestigious journal, Cell Metabolism, online April 7, 2015. Being overweight, especially around the abdomen or waistline, increases the chances of developing type 2 diabetes. The question many scientists are trying to answer is: why does obesity contribute to insulin resistance? In their previous work, the Winers demonstrate that immune cells inside abdominal fat cause the release of 'pro-inflammatory' chemicals, which make the body less sensitive to insulin, the hormone that regulates blood sugar levels. This is known as insulin resistance - a major trigger for type 2 diabetes. In this research, the focus shifted from the fat to the gut, where the Winers found that mice fed a high-fat, high-calorie diet had larger amounts of pro-inflammatory immune cells and less of the regulating cells which help end an immune response, than in normal mice. The researchers found this same result in 14 humans, seven of whom were obese. The high-fat diet induces inflammatory changes



in the immune cells in the bowel, upsetting the immune balance, which in turn sets off a chemical cascade, damaging the bowel wall, allowing bacterial products to leak into the blood stream. This leakage is what contributes to insulin resistance, when the cells can no longer respond to and use insulin effectively to stabilize blood sugar. "If we could block the pro-inflammatory immune cells at the very beginning of this process, we could treat the disease more effectively," reasons Shawn Winer, who is a gastrointestinal pathology fellow in the Laboratory Medicine Program at University Health Network (UHN). "By refocusing on the bowel, we open up many more therapeutic options as we already have a number of approved drugs available to treat an inflamed bowel." The researchers then targeted the bowel inflammation found in the obese mice with 5-ASA, or mesalamine, a commonly used drug to treat inflammatory bowel disease. They found that the drug reversed insulin resistance and lowered blood sugar significantly in the mice to near normal levels. "By using this drug, we found that we could prevent type 2 diabetes in mice," says Dan Winer, who is also an endocrine pathologist at UHN and an Assistant Professor in Laboratory Medicine and Pathobiology at the University of Toronto. "If this works in humans, it could change the whole field of diabetes prevention and treatment." He also points out that some medications targeting the bowel act locally in the gut, with minimal side effects and absorption in the rest of the body. More than two million Canadians have diabetes. Currently, those with diabetes lower their glucose through diet, exercise, anti-diabetic tablets or insulin injections (usually several times a day) and must regularly monitor blood glucose levels. High glucose levels result in damage to eyes, nerves and kidneys and increase the risk of heart attack, stroke, blindness, erectile dysfunction, foot problems and amputations. Many laboratories around the world are in a race to find alternative and effective ways to lower glucose levels because of the severe complications which can result from high sugar levels. The current findings of this paper point to changes in the bowel which can be targeted by new classes of potentially effective, minimal side-effect therapies for insulin resistance, a precursor to type 2 diabetes.

Mapleton, USA

Utah Teen Diagnosed With Rare Water Allergy

When Alexandra Allen was a little girl, she wanted to be a marine biologist and live on a sailboat. After being diagnosed with an allergy to water, the 17-year-old from Mapleton, Utah, said she realizes that dream isn't likely to come true. Allen said she had her first severe reaction to water when she was about 12. While on vacation with her family, she went swimming in a hotel pool and later that night woke up itching and covered in hives, she recalled. "I remember sitting in the bathroom

trying so hard not to scratch myself and make it worse until my mom came back with the Benadryl," the high school senior told ABC News. She said she assumed at first that she was allergic to chlorine or some other harsh chemical, so she avoided swimming pools. But she knew the problem was much larger when she broke out into hives after swimming in a lake known for having very clean water. When Allen was about 15 she came across a medical site that highlighted aquagenic urticarial, a condition defined by a painful reaction from skin contact with water as well as dry skin and dry eyes, she said, noting that it described her symptoms perfectly. And when she took it to her dermatologist, he agreed. "He brought in a few other doctors and they just sat around in awe," she recalled, adding that the test to confirm the diagnosis, which involved soaking in a tub of water, felt "like being tortured." Aquagenic urticarial is so rare that only about 50 cases have been described in medical literature, said Dr. Barney J. Kenet, a dermatologist with the Cornell Medical Center. "It's a real thing. We learn about it in medical school, though I have never seen a case in my practice," Kenet said. While not a true allergy, it causes severe allergy-like reactions, even after exposure to rain, snow, sweat or tears, according to an article in the Journal of Allergy Immunological Practice, one of the few studies to describe the disease. It tends to affect women more than men and usually first appears during puberty. The cause of aquagenic urticarial is not well understood, Kenet said. One theory is that the sweat glands within the skin produce a toxin that triggers the allergic response, he said. Or it could be that antigens that cause the immune system to produce antibodies are absorbed in the skin after dissolving in water to trigger the allergic reaction. Finding ways to avoid water has definitely been a challenge, Allen said. Obviously swimming is out. She has become a vegetarian to reduce the oils in her skin, avoids sweating and can only take two to three very short, cold showers a week, she said. Even humid climates can bring on a reaction, as she found out last year during a trip to Cambodia with a humanitarian aid group. Her condition is thought to be degenerative, meaning that it gets worse with time and repeated exposures, Allen said. She expects at some point that drinking water may become a problem. Last year, she spoke to a British woman with the same diagnosis who told her she can now only drink Diet Coke. But Allen said she remains positive. She tries to focus on the upside of her situation. "At least I'm not allergic to dogs -- and it does get me out of doing the dishes," she said. By Liz Neporent. The original article from the *Good Morning America*.

London, UK

Fossil of “Super Salamander” Species

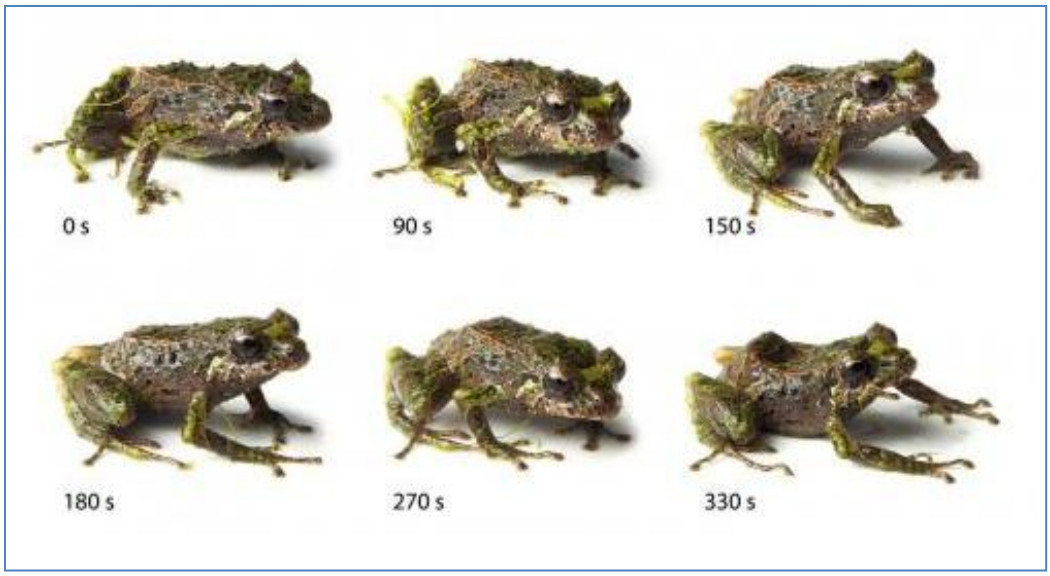
Fossil remains of a previously unknown species of a crocodile-like "super salamander" that grew as long as a small car and was a top predator more than 200 million years ago have been found in southern Portugal, researchers announced Tuesday. The species

grew up to two meters (six feet) in length and lived in lakes and rivers, University of Edinburgh researchers said. The team said the species, given the name *Metoposaurus algarvensis*, was part of a wider group of primitive amphibians that were widespread at the time but became extinct. They are the ancestors of modern amphibians such as frogs, and are believed by paleontologists to have lived at the same time the dinosaurs began their dominance. Steve Brusatte of the University of Edinburgh's School of GeoSciences, who led the study, said the new species, which had hundreds of sharp teeth, is "weird compared to anything today." It was at the top of the food chain, feeding mainly on fish, but it was also a danger for newly appeared dinosaurs and mammals that strayed too near the water, Brusatte said. The team says the find establishes that this group of amphibians lived in a more diverse geographic area than had been thought. Andrew Milner, an expert on early amphibians at the Natural History Museum in London who was not involved in the study, said the find "is another piece of the picture." The Portuguese site has "very good potential to give us more and different types of animal" from the Upper Triassic period, he added. The dig in Portugal began in 2009 and took several years. The "super salamander" bones were uncovered in a half-meter thick layer of rock in a hillside that is "chock-full" of bones, Brusatte said. The team hopes to raise funds to continue excavating the site.


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

ZOOLOGY, USA

Shape-shifting Frog Discovered in Ecuadorian Andes



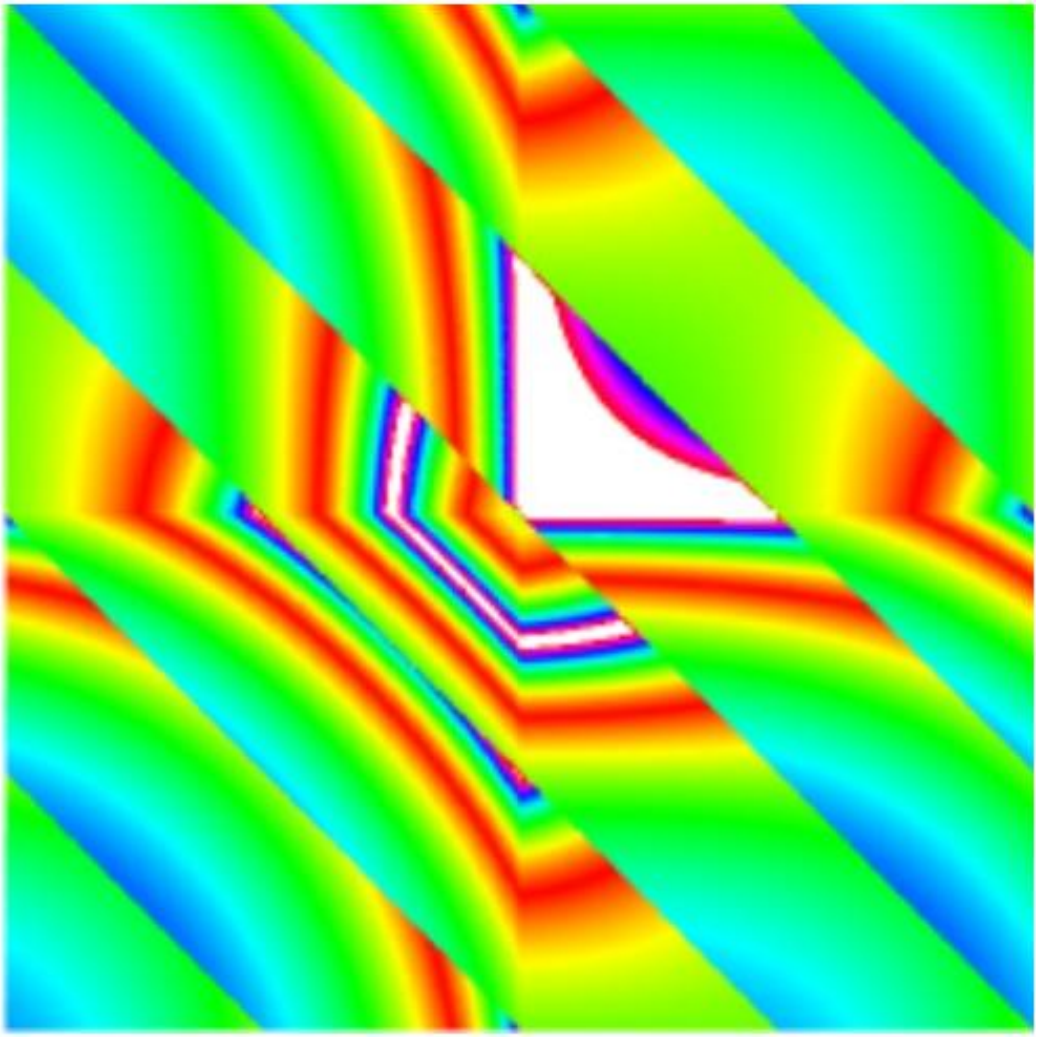
A frog in Ecuador's western Andean cloud forest changes skin texture in minutes, appearing to mimic the texture it sits on. Originally discovered by a Case Western Reserve University PhD student and her husband, a projects manager at Cleveland Metroparks' Natural Resources Division, the amphibian is believed to be the first known to have this shape-shifting capability. But the new species, called *Pristimantis mutabilis*, or mutable rainfrog, has company. Colleagues working with the couple recently found that a known relative of the frog shares the same texture-changing quality—but it was never reported before. The frogs are found at Reserva Las Gralarias, a nature reserve originally created to protect endangered birds in the Parish of Mindo, in north-central Ecuador. The researchers, Katherine and Tim Krynak, and colleagues from Universidad Indoamérica and Tropical Herping (Ecuador) co-authored a manuscript describing the new animal and skin texture plasticity in the *Zoological Journal of the Linnean Society*. They believe their findings have broad implications for how species are and have been identified. The process may now require photographs and longer observations in the field to ensure the one species is not mistakenly perceived as two because at least two species of rain frogs can change their appearance. Katherine Krynak believes the ability to change skin texture to reflect its surroundings may enable *P. mutabilis* to help camouflage itself from birds and other predators. The Krynaks originally spotted the small, spiny frog, nearly the width of a marble, sitting on a moss-covered leaf about a yard off the ground on a misty July night in 2009. The Krynaks had never seen this animal before, though Tim had surveyed animals on annual trips to Las Gralarias since 2001, and Katherine since 2005. They captured the little frog and tucked it into a cup with a lid before resuming their nightly search for wildlife. They nicknamed it "punk rocker" because of the thorn-like spines covering its body. The next day, Katherine Krynak pulled the frog from the cup and set it on a smooth white sheet of plastic for Tim to photograph. It wasn't "punk "—it was smooth-skinned. They assumed that, much to her dismay, she must have picked up the wrong frog. "I then put the frog back in the cup and added some moss," she said. "The spines came back... we simply couldn't believe our eyes, our frog changed skin texture! "I put the frog back on the smooth white background. Its skin became smooth." "The spines and coloration help them blend into mossy habitats, making it hard for us to see them," she said. "But whether the texture really helps them elude predators still needs to be tested." During the next three years, a team of fellow biologists studied the frogs. They found the animals shift skin texture in a little more than three minutes. Juan M. Guayasamin, from Universidad Tecnológica Indoamérica, Ecuador, the manuscript's first author, performed morphological and genetic analyses showing that*P. mutabilis* was a unique and undescribed species. Carl R. Hutter, from the University of Kansas, studied the frog's calls, finding three songs the species uses, which differentiate them from relatives. The fifth author of the paper, Jamie Culebras, assisted with fieldwork and was able to locate a second population of the species. Culebras is a member of Tropical Herping, an organization committed to discovering, and studying reptiles and amphibians. Guayasamin and Hutter discovered that *Prismantis sobetes*, a relative with similar markings but about twice the size of *P. mutabilis*, has the same trait when they placed a spiny specimen on a sheet and watched its skin turn smooth. *P. sobetes* is the only relative that has been tested so far. Because the appearance of animals has long been one of the keys to identifying them as a certain species, the researchers believe their find challenges the system, particularly for species identified by one or just a few preserved specimens. With those, there was and is no way to know if the ap-

pearance is changeable. The Krynaks, who helped form Las Gralarias Foundation to support the conservation efforts of the reserve, plan to return to continue surveying for mutable rain frogs and to work with fellow researchers to further document their behaviors, lifecycle and texture shifting, and estimate their population, all in effort to improve our knowledge and subsequent ability to conserve this paradigm shifting species. Further, they hope to discern whether more relatives have the ability to shift skin texture and if that trait comes from a common ancestor. If *P. mutabilis* and *P. sobetes*are the only species within this branch of Pristimantis frogs to have this capability, they hope to learn whether they retained it from an ancestor while relatives did not, or whether the trait evolved independently in each species.

MATHMATHICS, USA

Mathematicians Solve 60-Year-Old Problem

A team of researchers, led by Rensselaer Polytechnic Institute professor Yuri Lvov, has found an elegant explanation for the long-standing Fermi-Pasta-Ulam (FPU) problem, first proposed in 1953, investigated with one of the world's first digital computers, and now considered the foundation of experimental mathematics. The research, published today in the Proceedings of the National Academy of Science, offers a mathematical explanation for how a level of energy sufficient to produce one complete wave in an idealized chain of masses connected by springs is gradually distributed to thermal equilibrium. In this system, 32 masses (or particles) can move only left or right, and the energy in the system cannot dissipate through friction or heat. This system, famous among mathematicians and physicists, was introduced by Los Alamos



National Laboratory researchers Enrico Fermi, John Pasta, Stanislaw Ulam, and Mary Tsingou as a means to study how heat is conducted in solids and metals. At the time the researchers proposed the problem, they expected their numerical calculations would reveal that the system reaches a state of thermal equilibrium - similar to thermal equilibrium exhibited by gasses - in which the energy within the system is evenly divided among each possible movement (called "modes"). When the problem was first simulated with the Mathematical Numerical Integrator and Computer (MANIAC), one of the first digital computers, the researchers were puzzled to discover that after much iteration, energy within the system periodically dispersed and then concentrated to 97 percent of energy within a single mode. These phenomena became known as "FPU recurrence" and spawned a wealth of questions and research, in addition to thousands of research papers, becoming the foundation of experimental mathematics. Decades later, using far more powerful computers to run the simulation for greater lengths of time, researchers discovered that energy within the system did eventually reach equilibrium, but the question remained: how precisely was this happening? In the paper "Route to thermalization in the α-Fermi-Pasta-Ulam system," the researchers led by Lvov offer a simple and elegant explanation. According to their calculations, the key lies in a gradual transfer of energy during coincidences of six modes in the system. When precisely six modes interact, the energy is transferred in a nonreversible way. Over much iteration,

enough six-wave interactions occur, and enough energy is transferred, to reach complete thermal equilibrium. This conclusion is supported by extensive numerical simulations. "The key approach of our research is to consider the FPU system as a collection of resonantly interacting waves, in other words - waves interact in groups," said Lvov, a professor of mathematical sciences in the School of Science at Rensselaer Polytechnic Institute. "My collaborators and I have shown that interactions of triads, quartets, and quintets are reversible; in other words, they do not bring the FPU system closer to thermal equilibrium. However, the interaction of waves in sixtets does lead to irreversible transfer of energy. It takes the cooperation of six different waves to produce an interaction that is irreversible and, because of that, the process is extremely weak and very slow. That is why it takes so long to approach thermal equilibrium for the FPU system." Lvov researches in the area of mathematical physics and nonlinear phenomena, in particular the ocean internal and surface water waves. These systems can be viewed as complex systems composed of interacting particles or waves, which can be described under the general theoretical framework of "wave turbulence theory." Lvov seeks to further develop this theory and to use these developments to study such complex systems.

MEDICINE, USA

Child with Autism Improves with Antibiotic

John Rodakis, the parent of a child with autism was not looking to launch an international investigation into the microbiome (the collection of microorganisms that live on and in us) and autism, but, as he describes in his newly published article in the scientific journal Microbial Ecology in Health and Disease, when his young son's autism unexpectedly and dramatically improved while taking an antibiotic for strep throat, he began a quest to understand why. Following the surprise improvement, Mr. Rodakis, who in addition to being a parent is also a medical venture capitalist with a background in molecular biology and a Harvard MBA, began to examine the medical literature where he found a lone study from 1999 conducted at Chicago Rush Children's hospital that documented a similar phenomenon in autistic children. After speaking with other parents and clinicians he discovered that improvements on antibiotics such the one his son experienced were frequently observed, but not well studied. "I was determined to understand what was happening in the hope of helping both my son and millions of other children with autism." The Father's quest led him to world-renowned autism researcher Dr. Richard Frye, head of the Autism Research Program at Arkansas Children's Hospital Research Institute and his team and together they began a collaboration that grew to include other researchers from many different medical disciplines from all parts of the world. As the parent/researcher collaboration intensified, two ideas emerged: that the group should design a research trial to try to understand this unusual phenomenon and to hold a scientific conference on autism and the microbiome. "Careful parental observations can be crucial. In science we take these observations, put them through the scientific method, and see what we find. This is what can lead to ground breaking scientific discoveries and breakthroughs in the field", said Dr. Frye. This past June, the group held a first-of-its-kind conference: The First International Symposium on the Microbiome in Health and Disease with a Special Focus on Autism which was co-sponsored by Mr. Rodakis' newly formed non-profit N of One: Autism Research Foundation. As a result of that conference, a special issue on Autism and The Microbiome is being published in the peer-reviewed scientific journal, Microbial Ecology in Health and Disease. The issue features articles from confer

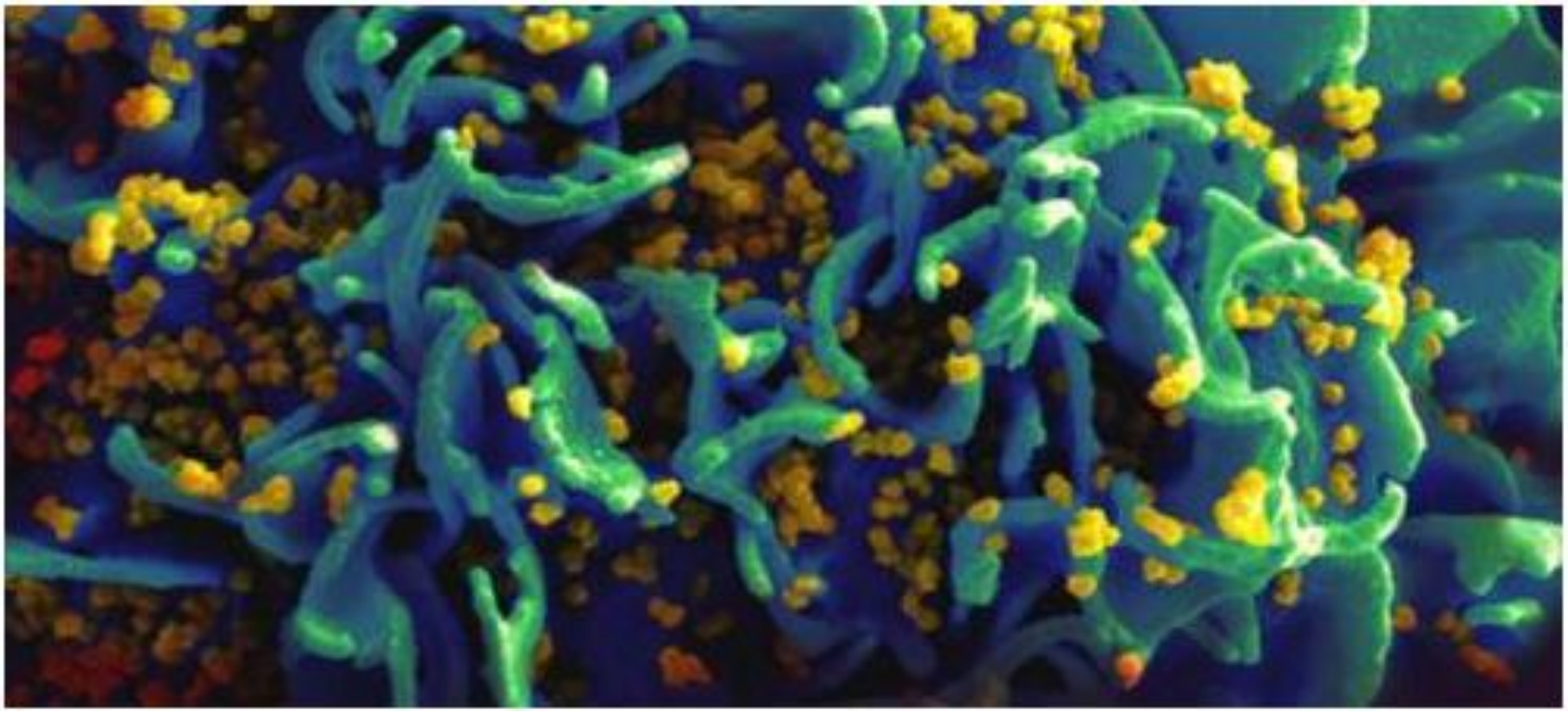
ence presenters and others including an article by Mr. Rodakis, titled "An n=1 case report of a child with autism improving on antibiotics and a father's quest to understand what it may mean." New evidence for the microbiome's involvement in autism spectrum disorder has been rapidly accelerating in recent years. Fifteen years ago, another autism parent, Ellen Bolte, had what at the time was a far-fetched hypothesis: that gut bacteria played a role in some cases of autism. Her efforts resulted in the 1999 small, but ground-breaking clinical trial conducted at Chicago Rush Children's hospital that Mr. Rodakis found while doing his research. Today, that hypothesis has grown into a large body of evidence demonstrating a link between the microbiome and autism, also called the "gut-brain" connection. Just this summer a team at Arizona State University led by Dr. Rosa Krajmalnik-Brown published findings repeating what others have documented that showed that children with autism exhibited less bacterial diversity in their guts than typically developing children. Dr. Krajmalnik-Brown, was also a speaker at the conference and also has a paper appearing in the special issue. In the article out this month, Mr. Rodakis outlines the personal story of how his child's autism symptoms improved while

taking a common antibiotic and then goes on to summarize recent human and animal-model research into possible biological mechanisms at work. Mr. Rodakis does not suggest that antibiotics are a treatment for autism, but rather may be useful as a research tool. Mr. Rodakis adds, "Current research is demonstrating that gut bacteria play previously undiscovered roles in health and disease throughout medicine. The evidence is very strong that they also play a role in autism. It's my hope that by studying these antibiotic-responding children, we can learn more about the core biology of autism." Mr. Rodakis argues that that the microbiome's role in autism is a promising area for further research, though under-funded by the current major public and private organizations that fund autism research. Mr. Rodakis' active efforts to shape and encourage research into promising areas is part of a broader trend of patients and affected families playing an increasing role in driving promising medical research. Mr. Rodakis argues that the link between the microbiome and autism is not just plausible, but given recent research, likely.

ONCOLOGY, USA

Brain Tumor Cells Decimated By Mitochondrial "Smart Bomb"

An experimental drug that attacks brain tumor tissue by crippling the cells' energy source called the mitochondria has passed early tests in animal models and human tissue cultures, say Houston Methodist scientists. As reported on the cover of the April 2015ChemMedChem (early online), Houston Methodist Kenneth R. Peak Brain & Pituitary Tumor Center Director David S. Baskin, M.D., and Peak Center Head of Research Martyn Sharpe, Ph.D. designed a drug called MP-MUS that destroyed 90 to 95 percent of malignant glioma cells, yet in other experiments did not seem to adversely affect healthy human brain cells (in vitro). This compliments a soon to be published extensive study showing the same drug can treat human brain cancer grown in the brains of mice. Researchers hope to begin testing the drug in human clinical trials in 2016 or 2017 "We are very optimistic that we'll get there," said Baskin, also Vice Chair of the Department of Neurosurgery at Houston Methodist Hospital. "Our past work has shown that MP-MUS has very low toxicity until it gets into tumor cells. Once it arrives, it is changed to its active form, doing a lot of damage where we want it to, leaving healthy brain cells alone—a bit like a 'smart bomb.' To our knowledge, this is the first known example of selective mitochondrial chemotherapy, which we believe represents a powerful new approach to brain cancer." Medical options for brain tumor patients are woeful, Baskin said. "It's a horrible diagnosis. Because of where the tumors are located, and because of the way they can infiltrate healthy tissue, surgery is often not helpful long term. The most effective chemotherapy drug available right now, temozolomide, only extends life from 9 to 15 months, and patients' quality of life during that period isn't very good." For that reason, Baskin said, he and researchers around the world have been looking for new treatment approaches, such as vaccines intended to aid the body's immune system's recognition and removal of tumor cells, gene therapy and, in the present case, targeting tumor cell mitochondria. Gliomas (a type of brain tumor) develop from brain cells called astrocytes. Gliomas account for as much as 20 to 30 percent of all tumors of the brain and central nervous system. Mitochondria are often referred to as the "powerhouses" of cells—including misbehaving cancer cells—because they help cells create energy. In cancer cells this feature is partially switched off, causing cells to rely on other systems that generate energy. The numerous pill-shaped mitochondria in each cell perform a number of other crucial functions, however, and even cancer cells cannot grow and divide without healthy mitochondria. As luck would have it, an enzyme called MAO-B is overexpressed in brain tumor cells, which is the target of MP-MUS. This means that healthy cells are only exposed to low levels of MP-MUS and their mitochondria to very low levels of P+-MUS, Baskin says. On the other hand, in tumor cells the vast majority of the prodrug is converted into P+-MUS, which essentially traps the drug inside their mitochondria where it attacks the mitochondrial DNA. "We found that we could achieve profound effects with MP-MUS at very low concentrations, around 75 micromolar," said Baskin, Professor of Neurological Surgery, Weill Cornell Medical College. "By contrast, temozolomide must be used at concentrations two to three times that to be of any use to patients. Our approach is designed to capitalize on what is going inside the cells. Tumor cells have much more MAO-B, and when challenged, make even more MAO-B as a sort of defensive response. We hope that we are one step ahead of the cancer cells, as we are using that very fact to kill them." The researchers reported MP-MUS's toxicity to healthy cells remained low at concentrations as high as 180 micromolar. This information will be useful to the researchers as they consider safety and efficacy trials in human patients. Houston Methodist and Baskin and Sharpe entered into an agreement with Virtici, LLC to develop MP-MUS and are currently preparing toxi-



cology studies which are required prior to clinical trials.

BIOLOGY, UK

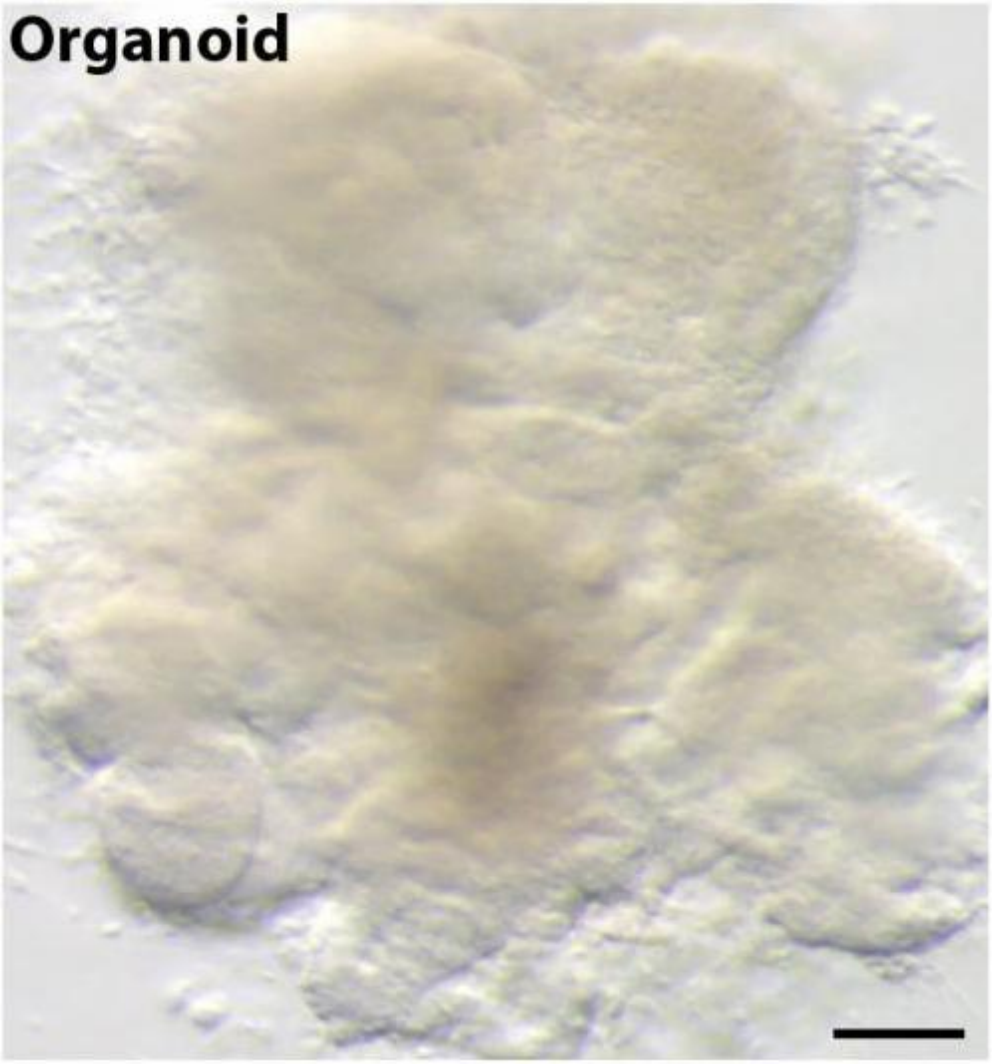
Blood Thinning Drug Helps in Understanding a Natural HIV Barrier

New research published today reveals how the protein langerin, which is present in genital mucous and acts as a natural HIV barrier during the first stages of contamination, interacts with the drug heparin. The research team has been able to identify two different mechanisms for that interaction - involving different sites or 'faces' at the surface of the langerin protein. Lead researcher Dr Jesus Angulo from UEA's school of Pharmacy said: "Langerin is produced by immune cells which are present in genital mucous. They constitute the first obstacle that the HIV virus finds in its way to infecting someone. "Heparin is widely used as an anticoagulant agent that prevents the formation of blood clots. But it is also occurs naturally in the body with different compositions and surrounds our cells. "Langerin-heparin interactions are thought to be important in the degradation of the HIV virus. The way that heparin interacts with langerin is important because it is thought to stabilize the formation of granules that facilitates the elimination of HIV particles. "This is a basic research study providing structural details of a potentially relevant interaction in a known natural barrier to HIV. Yet, of course, it doesn't mean that taking heparin or other anticoagulant drugs will protect people from HIV. "The ultimate aim of this line of research is to develop drugs that inhibit the HIV cellular receptors that facilitate infection, without inhibiting, or even better boosting, the activity of langerin. "This is obviously a long-term goal towards which this research is providing significant initial steps." 'Langerin-Heparin Interaction: Two Binding Sites for Small and Large Ligands as revealed by a combination of NMR Spectroscopy and Cross-Linking Mapping Experiments' is published in the *Journal of the American Chemical Society*.

BIOLOGY, USA

Scientists Coax Stem Cells to Form 3-D Mini Lungs

Previous research has focused on deriving lung tissue from flat cell systems or growing cells onto scaffolds made from donated organs. In a study published in the online journal eLife the multi-institution team defined the system for generating the self-organizing human lung organoids, 3D structures that mimic the structure and complexity of human lungs. "These mini lungs can mimic the responses of real tissues and will be a good model to study how organs form, change with disease, and how they might respond to new drugs," says senior study author Jason R. Spence, Ph.D., assistant professor of internal medicine and cell and developmental biology at the University of Michigan Medical School. The scientists succeeded in growing structures resembling both the large airways known as bronchi and small lung sacs called alveoli. Since the mini lung structures were developed in a dish, they lack several components of the human lung, including blood vessels, which are a critical component of gas exchange during breathing. Still, the organoids may serve as a discovery tool for researchers as they churn basic science ideas into clinical innovations. A practical solution lies in using the 3-D structures as a next step from, or complement to, animal research. Cell behavior has traditionally been studied in the lab in 2-D situations where cells are grown in thin layers on cell-culture



dishes. But most cells in the body exist in a three-dimensional environment as part of complex tissues and organs. Researchers have been attempting to re-create these environments in the lab, successfully generating organoids that serve as models of the stomach, brain, liver and human intestine. The advantage of growing 3-D structures of lung tissue, Spence says, is that their organization bears greater similarity to the human lung. To make these lung organoids, researchers at the U-M's Spence Lab and colleagues from the University of California, San Francisco; Cincinnati Children's Hospital Medical Center; Seattle Children's Hospital and University of Washington, Seattle manipulated several of the signaling pathways that control the formation of organs. First, stem cells - the body's master cells—were instructed to form a type of tissue called endoderm, which is found in early embryos and gives rise to the lung, liver and several other internal organs. Scientists activated two important development pathways that are known to make endoderm form three-dimensional tissue. By inhibiting two other key development pathways at the same time, the endoderm became tissue that resembles the early lung found in embryos. In the lab, this early lung-like tissue spontaneously formed three-dimensional spherical structures as it developed. The next challenge was to make these structures expand and develop into lung tissue. To do this, the team exposed the cells to additional proteins that are involved in lung development. The resulting lung organoids survived in the lab for over 100 days. "We expected different cells types to form, but their organization into structures resembling human airways was a very exciting result," says lead study author Briana Dye, a graduate student in the U-M Department of Cell and Developmental Biology.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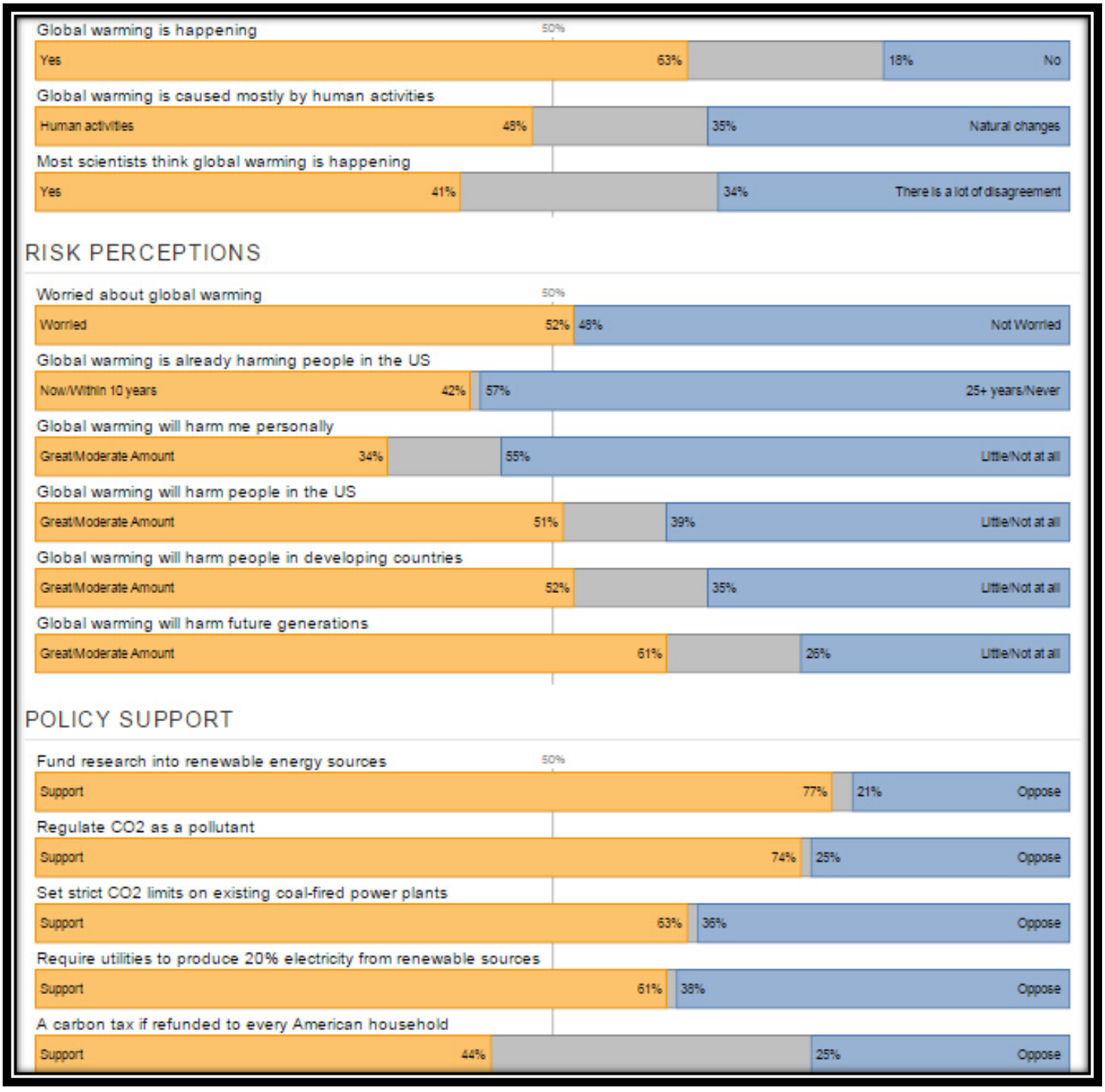
Estimated Percent of Adults Who Think Global Warming Is Happening



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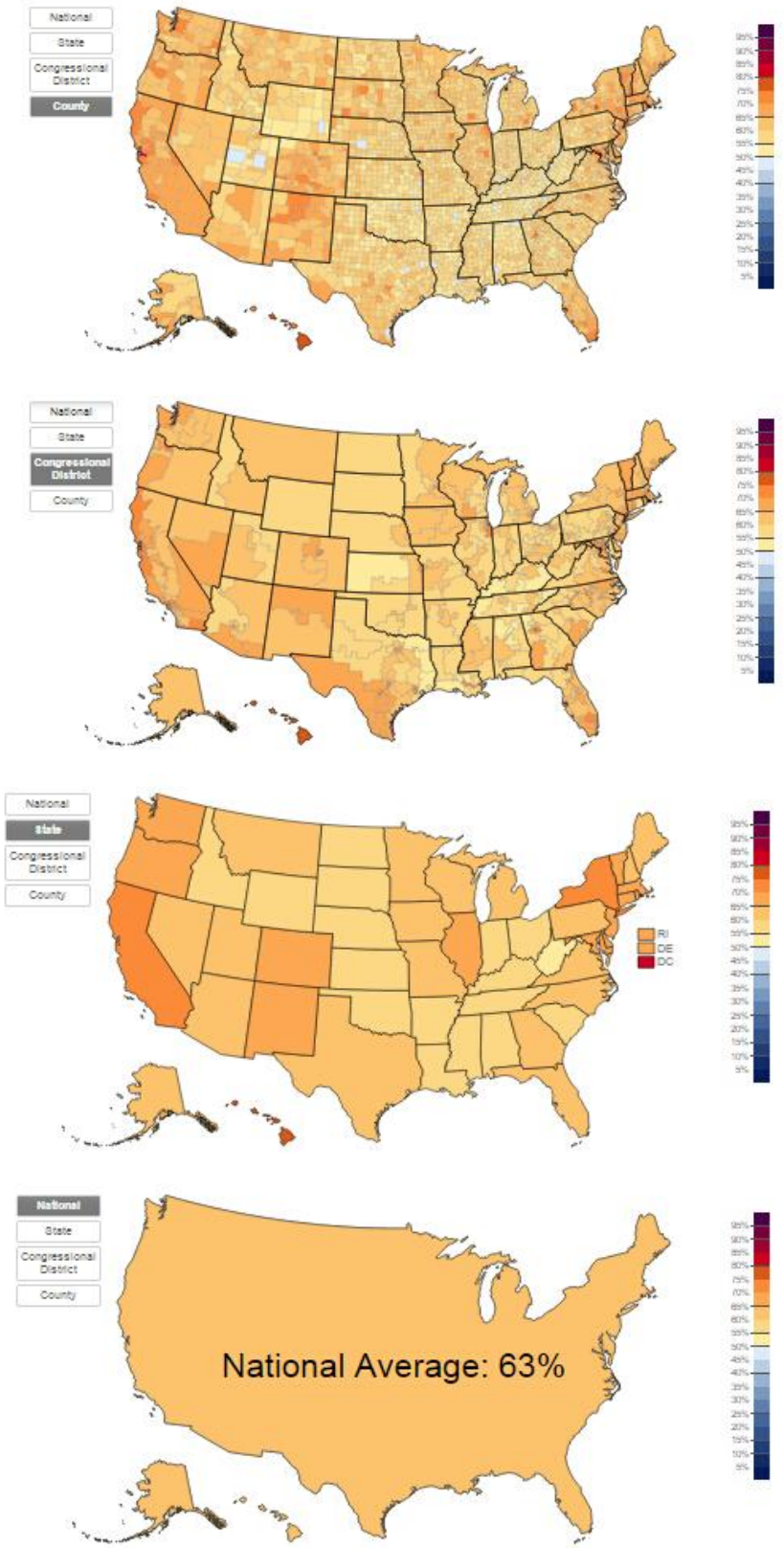

Public opinion estimates are produced using a statistical model based on national survey data gathered between 2008 and 2014 by the Yale Project on Climate Change Communication and the George Mason Center for Climate Change Communication. For details see methods and Howe, P., Mildenberger, M., Marlon, J.R., and Leiserowitz, A., "Geographic variation in opinions on climate change at state and local scales in the USA," Nature Climate Change. DOI: 10.1038/nclimate2583.


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

Aili Sunny, Senzhu Bao, Yusheng Liu, Maria L. Bolick, Mary K. Pathak, Fuzhou Wang

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

Aili Sunny,[*,1] Senzhu Bao,[†,1] Yusheng Liu,[‡,1] Maria L. Bolick,[*] Mary K. Pathak,[*] Fuzhou Wang[*,‡,Δ]

SUMMARY **Although pain is the most awful feeling for personal perception, it possesses critical benefits for preventing our human being to be injured further. Pain itself forms an overbalanced microenvironment in which people undertakes individualized changes in its neurobiological, psychological, endocrinological and genetic properties especially in the context of chronic pain or when the acute pain transmitted to chronicity. Our previous part (Part I) review the general epigenetic modification of nociceptive contributing factors in the context of chronic pain. Herein (Part II) we paid specific attention on the epigenetic regulation of pain-associated molecules including neurotransmitters and other factors. A detailed understanding of the specific modulating factors that influence individual epigenetic differences contributing to pain sensitivity and responsiveness to analgesics possesses essential implications in clinical pain management.■**

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*: Division of Neuroscience, Bonoi Academy of Science and Education (BASE), Winston-Salem, NC 27103, USA

†: Department of Stomatology, Affiliated Hospital of Qinghai University, Xining 811600, Qinghai, China

‡: Department of Anesthesiology, Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, Nanjing 210004, Jiangsu, China

1: These authors contributed equally to this work.

Δ: Correspondence to: Dr. Fuzhou Wang, Tel: +1-336-734-3247, Email: zfwang50@njmu.edu.cn Or fred.wang@basehq.org

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Keywords: Pain – Gene expression – Epigenetics – Analgesia – Neural inhibition

PAIN IS a don't-want-to-be experience no matter at which context it is, either at the acute postoperative phase or when it becomes chronicity, even though it possesses function of further-injury avoidance. Different types of therapeutic maneuvers, physiologically and physically, have been developed to control the overbalanced pain, whereas the effectiveness of these methods is limited (1, 2). Facilitation and inhibition are two major compositions of the pathway of pain transduction that draws much attention on in the past decades (3, 4), and great progress was made based on these two "yin" and "yang" systems. However, our patients with pain are still suffering from the "God-made original sinful perception" without efficient conquers. 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.

Epigenetic Regulations of Pain

Pain as one of the major stressors can evoke physiological and psychological changes that induce alterations in the expression of pain-associated molecules (5). Under the stimulation of pain, different molecules and proteins showed different levels of expression that finally forms a complex molecular matrix. This is the determinant whether the pain will tend to recover or to get worsened. However, who was the underlying controller of the molecular expression, and further how they reached such a precise interaction? Emerging evidence suggests that epigenetic modulation operates the expression of different genes in the context of pain (6). Given peripheral and central sensitizations are two major parts of the pathogenesis of pain (7, 8), we herein describe their relationship between epigenetic mediation separately, but the de-facto relationship should be in combination.

Epigenetics and Peripheral Sensitization

In most cases, pain derives from peripheral tissue injury or diseases that would unavoidably result in injury on the nociceptors or neural trunks. A series of responses, physically and physiologically, will follow up and then the self-adjustment is activated to avoid further injury and to control the propagation of pain (9). This is the typical process of peripheral injury induced pain. One pivotal step of the pain occurrence is the newly generated mediators that were released by the injured tissues, recruited immune cells and peripheral neurons (10). The injury-induced peripheral pro-analgesic mediators include pro-inflammatory cytokines (TNF-α, IL-1β), chemokines (CCL2, CCL3, and CXCL5), prostanoids (PGE_2, PGI_2), nerve growth factor (NGF), bradykinin, histamine, platelet-activating factor, nitric oxide (NO), and proton (H^+) (11-13). Once these mediators were released due to tissue injury, they will activate and sensitize the nociceptors making them spontaneously active and more readily to be activated by sub-threshold stimuli. We will discuss the epigenetic regulation on these peripheral pain-related mediators.

TNF-α and IL-1β are two typical pro-inflammatory cytokines believed released and upregulated in response to tissue injury. In arthritic patients, HDAC inhibitors have been observed producing substantial clinical benefits and the levels of both TNF-α and IL-1β were significantly reduced upon the using of HDAC inhibitors (14, 15) indicating that the expression of peripheral inflammatory cytokines is regulated by epigenetic mechanisms. In further, bindings of IL and TNF-α to their respective receptors lead to H4 hyperacetylation of other factors' promoters via affecting NF-κB pathway (1616). Besides, the recruitment of NF-κB to pro-inflammatory genes was affected by H3K4 methylation (17). CCL2 excited primary sensory neurons by acting on the biophysical properties of Na(v)1.8 currents via a CCR2/Gβγ-dependent mechanism (18), and in consideration of the strong association between the changes in function of voltage-gated sodium channels in nociceptive primary sensory neurons participating in the development of peripheral hyper-excitability, and then CCL2 was considered as one important contributor of peripheral sensitization. Meanwhile, CCL2 enhanced striatal dopamine release by cognating to CCR2 receptor through extracellular signal-regulated kinase (ERK), a fundamental enzyme in striatal gene and epigenetic regulation (19), to sensitize cocaine (20) suggesting that chemokine activation is an essential component of peripheral sensitization that may be closely related to epigenetic regulation. As the target of COX inhibitors, PGE_2 and PGI_2 are two contributors to peripheral hyperalgesia. Emerging evidence showed that epigenetic alterations play a critical role in the regulation of the genes of the COX pathway (21), and also the epigenetic processes underlying expression of the prostanoid receptor EP2 were characterized (22) demonstrating that COX-PGE_2-EP2 pathway is affected by epigenetic modulation. NGF, a small secreted protein, is critical for the growth, maintenance, and survival of target neurons. Brain-derived neurotrophic factor (BDNF) is the most studied NGF, and a large number of data documented its involvement in the regulation of pain (23). However, the expression of BDNF in the CNS was regulated by the interaction between MeCP2 and SIRT1, two critical epigenetic mediators (24), showing that an association between NGF and epigenetic exists. Bradykinin, histamine, platelet-activating factor and NO are four important inflammatory mediators released by injured tissue cell, blood vessels, and blood cells (12), and they contributed to the formation of peripheral inflammation soup around the injured area. Immuno-reactivity of HDAC 8 was detected in the histamine neurons with a pericellular pattern (25), NO itself is an essential mediator of epigenetic gene expression (26) and the NO population was affected by DNA methylation in arginases 1 and 2 (27) suggesting that these tissue-derived mediators also may be regulated by the epigenetic mechanisms. Although we thus far have evidence indicating the epigenetic regulation on the peripheral sensitization, it is still infancy and in-depth work is needed in elucidating the epigenetic modulation on their expression and the potential intertalk amongst them each other.

Epigenetics and Central Sensitization

Central sensitization is defined as an increased response to stimulation that is mediated by amplification of signaling in the CNS (7, 8). Neuroplasticity, glia activation, ion channels' expression and states, and neurotransmitters balance all are critical contributors to the central sensitization (28), a pathological state in which merely the subthreshold stimulation or even no-stimulation (i.e. spontaneously) causes pain. The persistence of pain itself is a risk factor in inducing central sensitization, through which a vicious cycle formed only if when the pain was effectively treated. A great progress has been being made on the understanding of pain mechanisms on the basis of central sensitization, whereas the therapeutic efficacy with currently available methods is limited (29). Traditional concept is that seeking and finding potential contributors to the pathogenesis of pain, and then figuring out activating or inhibiting molecules on the target players. Based on this, over hundreds of molecules were identified over the past decades, but we still cannot reach the ideal purpose – conquer the pain with easy-to-use method. What is the outlet for the next step in pain study? For this question, the epigenetic modulation may give us hope.

Both systemic and spinal administration of HDAC inhibitors produced analgesic effects in inflammatory pain models (30), and such effect resulted from the expression changes of the mGluR2 receptor in both DRG and spinal cord (31). Moreover, pain itself evoked epigenetic changes in pro-analgesic genes. The down-regulation of glutamic acid decarboxylase 65 (GAD65) and hypoacetylation at its promoter were detected when complete Freund's adjuvant (CFA) was injected into rat's paw or the spinal nerve was ligated (32). Chronic pain conditions are strongly associated with the changes in brain structure and cortical function, but these changes are mediated by the reversible DNA methylation in the mouse prefrontal cortex (33). The increased monocyte chemotactic protein (MCP-3) expression associated with IL-6 dependent epigenetic modification at the MCP-3 promoter after nerve injury plays a critical role in the neuropathic pain-like state (34). Promoter demethy-lation of cystathionine-β-synthetase gene, the enzyme promoting synthesizing hydrogen sulfide, contributes to inflammatory hyperalgesia through protein kinase A (PKA) pathway (35). Nonetheless, the increased global DNA methylation and methyl-CpG-binding protein 2 (MeCP2) expression in the spinal cord after nerve damage plays an important role in neuropathic pain (36). Hyperacetylation of histone H3 on the promoter regions of macrophage inflammatory protein 2 (MIP-2) and C-X-C chemokine receptor type 2 (CXCR2) evoked chronic neuroinflammation by neutrophil accumulation resulting in neuropathic pain (37). These above-mentioned findings demonstrate that pain can induce DNA or histone methylation and demethy-lation, or/and histone hyperacetylation and hypoacetylation of specific genes, and then these epigenetic alterations either deteriorate or alleviate pain. What is the final effect therefore depends on the epigenetic balance.

Opioidergic alterations under the chronic pain condition were considered as an essential contributor to central sensitization (38), and corresponding epigenetic modification was proposed to be one of the underlying mechanisms. Chronic use of opioid increased methylation at a CpG rich island in the OPRM1 gene coding for MOP and at a global methylation site (LINE-1) in leukocytes, of which strongly associated with the increased clinical pain (39). However, ultra-low-dose naloxone provides clinical valuable for neuropathic pain management through regulating global histone methylation suggesting that either the opioid-induced hyperalgesia or pain-induced opioidergic impairment; epigenetic modification is the potential controller (40). Furthermore, epigenetic upregulation of NGF activity in the central nucleus of the amygdale (CeA) promoted the behavior of opioid reward and increased the sensitivity to the rewarding effect of subsequent opioids (41). How to reach the ideal state and how to keep the balance of opioidergic function via adjusting epigenetic regulation and other pain-modulating systems still need to be investigated.

Epigenetic Mechanisms of Pain – Future Directions

Although we so far have evidence for the correlation between epigenetic modification and pain, it just dawns on us. We hereby hypothesized that pain was a three-dimensional bio-phenomenon that includes physical, physiological and psychological changes, in which the tissue injury including chemical, physical, biological and disease-associated ones belongs to the physical dimension, and the molecular and cellular changes including peripheral and central alterations belong to the physiological dimension, and the changes in spiritual and mood belong to the psychological dimension. How to teasing out the precise relationship among these three facets and epigenetic modulation is a thorny challenge for pain scientists.

The interacting matrix among different kinds of pain-related molecules at the peripheral site and in the CNS and different types of epigenetic regulators is the actual situation under the condition of pain. Figuring this complex is as difficult as mapping human disease spectrotyping, while it promises us the final solution of pain therapy. We cannot explore this with a once-for-all pattern, but the step-by-step investigation is

the feasible way in tapping the interactions between two or three these molecules. Good examples are as follows: nerve injury caused a marked reduction in the acetylation of histone H4 at K(v)4.3-neuron-restrictive silencer element (NRSE) through transcriptional suppressor neuron-restrictive silencer factor (NRSF) in the DRG (42), which depicted the crosstalk among histone acetylation, NRSE, K(v)4.3 and nerve injury in DRG; in addition, nerve injury diminished the activity of the big conductance Ca^{2+}-activated K^+ (BK) channel in small and medium DRG neurons by increased BDNF through epigenetic and transcriptional mechanisms (43), which mapped the interaction among BK channel, BDNF, epigenetic modulation and nerve injury in DRG; and further the histone acetyltransferase E1A binding protein p300 epigenetically mediated chronic constriction injury (CCI) induced neuropathic pain via upregulating COX-2 expression in the spinal cord (44), which showed the interrelationship among p300, COX-2, histone acetylation and nerve injury in the spinal cord. Therefore, great efforts are needed to map the complex.

No matter what mechanisms can be explored, the ultimate purpose is to reveal novel targets for pain management. Although the currently approved HDAC inhibitors as drugs like valproic acid for epilepsy and SAHA and FK228 for T cell lymphoma (45, 46) have been tested in animal models of pain, their effects on patients need to be observed at length. These global inhibitors of HDACs would unavoidably produce unexpected side effects, so the risks and benefits should be weighed before giving for pain control. This also raises the question that more specific therapeutics focusing on different epigenetic modulations are necessary for the treatment of pain. For the precise relationship amongst above-mentioned molecules and epigenetic mediators, the methods from the computational biology, such as molecular docking and packing, quantitative structure-activity relationships (QSAR), Monte Carlo simulated annealing approach, structural bioinformatics, pharmacophore modeling, and signal peptide prediction etc. may provide insights into corresponding molecule-molecule interactions and give hope for the development of novel therapeutics for pain.

In conclusion, the emerging evidence indicates that epigenetic modulation is an essential contributor to the pathogenesis of pain. The study on epigenetic control of pain is still infancy, efforts are needed and a new avenue will be opened along with the progress in the exploration of epigenetic-associated modulation of pain.

Conflict of Interests

None

Acknowledgements

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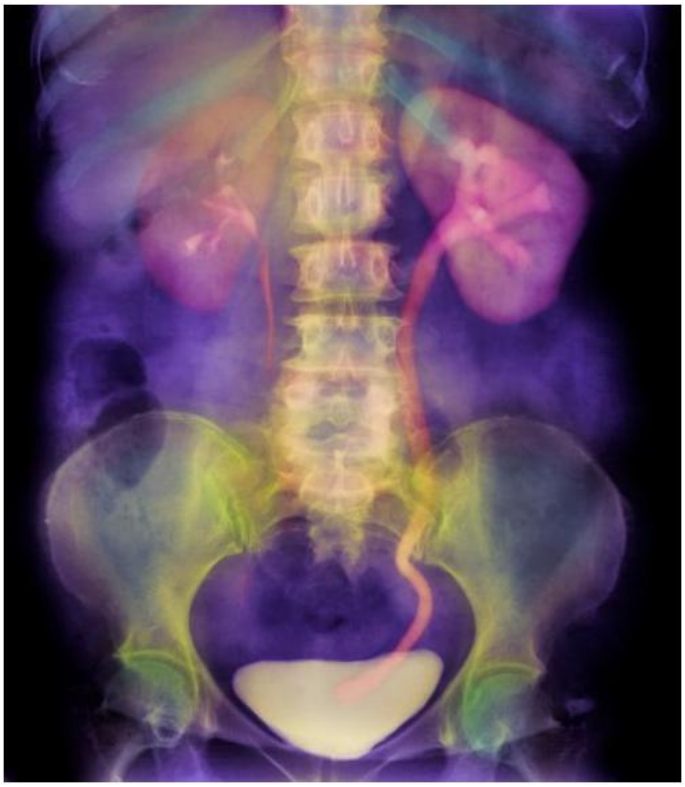
Who feeds us?


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

Nine Kidney Stone Myths to Stop Believing

By Ashley Macha (USA)

Getting a kidney stone is no walk in the park. And the rumors floating around about what to expect when the stone actually passes are not for the faint of heart. But, that's just what some of them are — rumors. So how can you be certain the pain you're experiencing is legitimately a kidney stone? What's the difference between a kidney stone versus appendicitis versus a urinary tract infection — or even a good old-fashioned stomachache? That's why it's important to know what you're dealing with, says Mantu Gupta, MD, director of The Kidney Stone Center at Mount Sinai Hospital, who comes across a lot of misconceptions when it comes to signs, symptoms, feel, and care of kidney stones.



According to a recent study in European Urology, kidney stones affect about one in 11 people in the United States, so it's becoming increasingly important to understand the signs and causes of kidney stones. Hallmark signs vary, but can include painful urination, nausea or vomiting, persistent need to urinate, fevers and chills, and pain that comes in waves and fluctuates in intensity. Think you know your stuff when it comes to preventing and spotting kidney stone symptoms? Here are nine myths to be aware of:

Myth No. 1: Drinking cranberry juice will help flush out the kidney stone.
Fact: Cranberry juice might actually make your kidney stones worse.

"It is good for preventing urinary tract infections, because it does solidify the urine and prevent infections, but it has the opposite effect with kidney stones," Gupta tells Yahoo Health. "Cranberry is high in oxalate [which can cause kidney stones], so we recommend not to drink cranberry juice or take supplements."

Myth No. 2: Getting a kidney stone feels like a stomachache.
Fact: Getting a kidney stone actually feels similar to a contraction — and some patients say the pain can be more severe than labor, says Gupta. The pain is typically colicky, coming in waves for intervals at a time. It can range from a sharp, stabbing sensation, to the sort of pain that comes from menstrual cramps, says Gupta.

Myth No. 3: You feel the pain in your lower back, where your kidneys are located.
Fact: The pain actually originates a little lower in the abdomen or gut, after the kidney stone passes into the ureter.
"The reason it hurts is that it's like a cork going down your ureter, which is shaped as a funnel and gets skinnier as you get to the bladder," says Philip Buffington, MD, chief medical officer of The Urology Group in Cincinnati, Ohio. The kidney stones then start to block the flow of urine and, if enough time passes, can cause the kidney to descend, causing terrible pain and nausea.

Myth No. 4: Drinking milk, which has calcium, will cause kidney stones.
Fact: Calcium is not the enemy.
"Many people are causing kidney stones because they have a lack of calcium in their diet," says Gupta. He suggests having a glass of milk or yogurt with your meal and consuming foods with magnesium, which will help bind the oxalate and help prevent kidney stones.

Myth No. 5: You'll pass multiple kidney stones.
Fact: Kidney stones can be multiple OR single stones.
Most of the time it's just one stone, especially if it's your first time experiencing one, Buffington tells Yahoo Health. But once you've passed a kidney stone, you're 90 percent more likely to pass another stone within 4 years. He suggests getting an ultrasound from your physician to help detect what you're dealing with.

Myth No. 6: It only takes a few hours for a kidney stone to pass.
Fact: Most people pass their stone within two to three days.
"If they're relatively comfortable, a patient can wait four to six weeks for it to pass through — but some patients come back years later," says Buffington. "They've stopped having pain, but a year later we see them and their kidney is smaller and starting to lose function." Just another good reason to consult a physician, even if time and pain passes.

Myth No. 7: Drinking soda can cause kidney stones.
Fact: Drinking fluids with phosphoric acid and high sodium levels can cause kidney stones.
It's not cola itself that causes kidney stones, but an ingredient in cola called phosphoric acid that can lead to an increased risk of kidney stone formation, says Gupta. Cola is also a diuretic, which can make your urine more concentrated with salt and promote kidney stones.

Myth No. 8: High-oxalate foods can cause kidney stones.
Fact: While an excessive amount of consumption of oxalate foods, paired with factors like dehydration, high sodium levels, and high calcium levels in the urine, *can* cause kidney stones, most kidney stones are linked to genetics.
And people who follow a diet that includes high oxalate foods can inhibit production of kidney stones by drinking water, reducing their salt intake, adding citrus to their diet, and reducing consumption of animal products.

Myth No. 9: Kidney stones look like small, grey pebbles.
Fact: Kidney stones can come in all shapes, sizes, colors, and textures.
Kidney stone patients might pass just one grain-sized stone, multiple grain-sized stones, smooth, pearl-shaped stones, jagged yellow stones, or even brown, golf-ball-sized stones. Gupta recommends capturing the stone and bringing it to your physician for analysis. The composition of the stone can help determine what caused the stone in the first place to prevent future stones from forming. By Ashley Macha. The original article from the Yahoo Health.

Science INSIGHTS®

The Official Journal of The Bonoi Academy of Science & Education (BASE)

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FREEDOM

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Meeting abstract:
Toro L, Singh H, Stefani E, Bopassa JC. NS1619-induced cardioprotection against ischemia reperfusion injury is lost after kcnma1 gene ablation (Abstract). A154, ASA 2012 Annual Meeting, Washington DC.

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