對外合作組織與機構動態報導

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ARGONNE X-RAYS USED TO HELP IDENTIFY A KEY LASSA VIRUS STRUCTURE

發現拉薩病毒的關鍵結構，阿岡實驗室先進光子源扮演重要角色

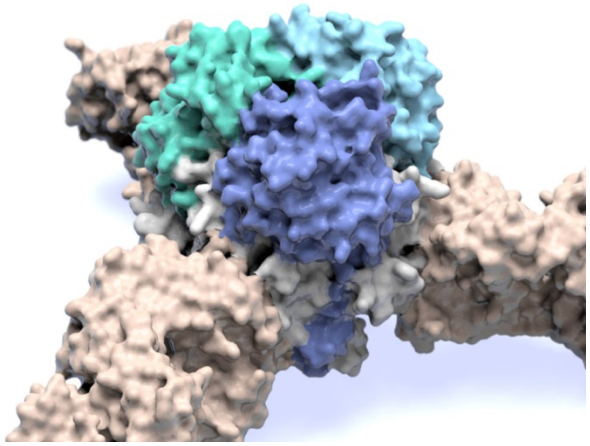
June 13, 2017

Before Ebola virus ever struck West Africa, locals were already

報告摘要(KEY INFORMATION)

1. 早在伊波拉病毒爆發之前，拉薩病毒已經在西非流行，致死率約 50-70%，每年奪走上千人性命。目前該病毒尚無解藥或疫苗可預防，而今年六月刊登在《科學》期刊上的新研究解出該病毒入侵人體的關鍵醣蛋白結構，將可能有助於疫苗之開發。
2. 近年來，日本國內採行了多樣措施以擴大氫能使用，研究學者並針對氫能相關科技如燃料電池汽車、燃料電池、氫能發電等進行研究。然而，如能在更宏觀的基準下進行社會建設，成效可望更佳。本文以氫能市鎮的建設為前提，討論、分析其成效。
3. 瑞士於 5 月 21 日舉行 2050 能源政策公投，支持修訂後能源行動方案者佔 58% 過半，將逐步採行可再生能源，走向非核願景。南韓第 19 任總統文在寅甫上任即宣布能源政策的未來方向，目前已停止所有新建核電廠計畫。
4. 一研究團隊指出可能兼顧成本效益並可預防愛滋病爆發的四種方法：預防性投藥 PrEP、鴉片類藥物替代治療 OAT、舊針換新針、檢驗治療計畫等；以結合 OAT 和舊針換新針的方案成效最佳。
5. 日常生活裡常發生這類不起眼的事件：你端著一杯滿滿的飲料，穿過人多擁擠的房間，忽然有人碰撞到你的手，不到半秒之內，你端飲料的手已經極其細微地調整了平衡，避免飲料打翻的慘劇。——研究發現大腦不參與這樣的刺激與反射之機制，將有助於義肢手臂受意念控制之研發。

on the lookout for a deadly pathogen: Lassa virus. With thousands dying from Lassa every year – and the potential for the virus to cause even larger outbreaks – researchers are committed to designing a vaccine to stop it.



Like Ebola virus, Lassa fever starts with flu-like symptoms and can lead to debilitating vomiting, neurological problems and even hemorrhaging from the eyes, gums and nose. The disease is 50 to 70 percent fatal – and up to 90 percent fatal in pregnant women.

“Hundreds of thousands of people are infected with the virus every year, and it is the viral hemorrhagic fever that most frequently comes to the United States and Europe. This structure gives you the blueprints to make a vaccine that would deliver antibody protection.”

Now a team led by Kathryn Hastie and Erica Ollmann Saphire at The Scripps Research Institute has solved the structure of the viral machinery that Lassa virus uses to enter human cells. Their study, published earlier this month in the journal Science, is the first to show a key piece of the viral structure, called a surface glycoprotein, for any member of the deadly arenavirus family, which also includes Ebola virus.

Research done at the Advanced Photon Source (APS) at the U.S. Department of Energy’s (DOE) Argonne National Laboratory was vital to the process of identifying the structure, which provides a guide for designing a Lassa virus vaccine.

“Studying Lassa is critically important. Hundreds of thousands of people are infected with the virus every year, and it is the viral hemorrhagic fever that most frequently comes to the United States and Europe,” said Ollmann Saphire, senior author of the new study. “This structure gives you the blueprints to make a vaccine that would deliver antibody protection.”

Success in solving the structure

The researchers solved this structure of the Lassa virus glycoprotein using a technique called X-ray crystallography, in which researchers prompted protein molecules from the virus to align and form a crystal. When X-rays hit the electrons in the crystal, they created diffraction patterns that revealed the organization of the crystal and the molecular structure of the protein that formed it.

Hastie used the powerful X-ray beams at the APS at early, critical stages of the project. During that phase, the team was working with very small crystals of the protein, crystals that were extremely hard to manipulate and study.

“It was the data that came from the APS that really allowed us to continue the project,”

Hastie said. “We needed the powerful detectors and flux at the APS, which allowed us to develop models and put us on the path toward building out the structure.”

Detectors at the APS measure the scattered X-rays, while the flux refers to the strength of the light source.

In addition to using the APS, researchers conducted experiments at the Stanford Synchrotron Radiation Lightsource at the DOE’s SLAC National Accelerator Laboratory.

During the project, the researchers quickly found that Lassa virus posed a challenge for X-ray crystallography. The technique depends on having a stable protein, yet all the Lassa virus glycoprotein wanted to do was fall apart.

The problem was that glycoproteins are made up of smaller subunits. Other viruses have bonds that hold the subunits together, “like a staple,” Hastie said. Arenaviruses don’t have that staple; instead, the subunits float away from each other. Another challenge was isolating those subunits to be able to study them. The researchers to recreate part of the viral lifecycle in the lab – a stage when Lassa’s glycoprotein gets clipped into those two subunits. “We had to figure out how to get the subunits to be sufficiently clipped and how to stabilize them to make sure that they stayed together,” Hastie said.

To overcome these obstacles, Hastie created mutant versions of important parts of the molecule and engineered a version of the Lassa virus surface glycoprotein that didn’t fall apart. She then used this model glycoprotein as a sort of magnet to find antibodies in patient samples that could bind with the glycoprotein to neutralize the virus.

At last, she solved the structure of the Lassa virus glycoprotein, bound to a neutralizing antibody from a human survivor.

Hastie’s structure showed that the glycoprotein has two parts. She compared the shape to an ice cream cone and a scoop of ice cream. A subunit called GP2 forms the cone, and the GP1 subunit sits on top. They work together when they encounter a host cell. GP1 binds to a host cell receptor, and GP2 starts the fusion process to enter that cell.

The new structure also showed a long structure hanging off the side of GP1 – like a drip of melting ice cream running down the cone. This “drip” holds the two subunits together in their pre-fusion state.

Zooming in even closer, Hastie discovered that three of the GP1-GP2 pairs come together like a tripod and are likely situated this way on the outside of the virus. This arrangement appears to be unique to Lassa virus. Other viruses, such as influenza and HIV, also have three-part proteins (called trimers) on their surfaces, but their subunits come together to form a pole, not a tripod.

“It was great to see exactly how Lassa was different from other viruses,” said Hastie, 10 years after starting the project. “It was a tremendous relief to finally have the structure.”

The crystallography work at Argonne was done on the National Institute of General Medical Sciences and National Cancer Institute Structural Biology Facility at the APS, or GM/CA-XSD. Additional contributions came from the Structural Biology Center, or SBC-CAT, which is supported by the DOE Office of Science.

“The GM/CA beamlines provide intense X-rays in a very small beam, which is ideal for studying very small crystals or portions of larger, imperfect crystals, said Robert Fischetti, the GM/CA-XSD Group Leader in Argonne’s X-Ray Science Division, and Life Sciences Advisor to the APS Director.

“GM/CA provides users with a combination of advanced hardware and software tools to systemically probe and collect data from such challenging samples in a user-friendly, powerful interface to study critically important biological problems,” he said.

Moving forward with a Lassa vaccine

Ollmann Saphire said using these X-ray tools provides the critically important step of visualizing the correct form of the viral glycoprotein. Because proteins can vary so much, having this visualization can aid in the step to design lifesaving vaccines.

The tripod arrangement of the Lassa surface glycoprotein offers a path for vaccine design. The scientists found that, in patients who have been infected with Lassa, 90 percent of the effective antibodies naturally produced by the patients’ immune systems targeted the spot where the three GP subunits came together. These antibodies locked the subunits together, preventing the virus from gearing up to enter a host cell.

A future vaccine designed to prompt the immune system to target Lassa’s glycoprotein would likely have the greatest chance of success if it could trigger the body to produce antibodies to target the same site.. As director of the Viral Hemorrhagic Fever Immunotherapeutic Consortium, Ollmann Saphire is already coordinating with her partners at Tulane and Kenema to bring a vaccine to patients.

The Coalition for Epidemic Preparedness Innovations, an international collaboration that includes the Wellcome Trust and the World Health Organization as partners, has recently named vaccine development for Lassa virus as one of its three top priorities. “The community is keenly interested in making a Lassa vaccine, and we think we have the best template to do that,” said Ollmann Saphire.

She added that with Hastie’s techniques for solving arenavirus structures, researchers can now get a closer look at other hemorrhagic fever viruses, which cause death, neurological diseases and even birth defects around the world.

In addition to Ollmann Saphire and Hastie, authors of the study, “Structural basis for antibody-mediated neutralization of Lassa virus,” were Michelle A. Zandonatti of The Scripps Research Institute; James E. Robinson and Robert F. Garry of Tulane University; Lara M. Kleinfelter and Kartik Chandran of the

Albert Einstein College of Medicine; and Megan L. Heinrich, Megan M. Rowland and Luis M. Branco of Zalgen Labs.

The study was supported by the National Institutes of Health and an Investigators in Pathogenesis of Infectious Diseases Award from the Burroughs Wellcome Fund.

The Advanced Photon Source and Stanford Synchrotron Radiation Lightsource are both DOE Office of Science User Facilities.

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THINKING ABOUT HYDROGEN TOWN- ENERGY SYSTEM AS SOCIAL INFRASTRUCTURE

氫能市鎮

By Harumi Hirai, Yoshiaki Shibata, Ryohei Ikarii, Lu Zheng, and Yasuaki Kawakami

Summary

As various initiatives have been taken for expanding hydrogen use in Japan in recent years, researchers have conducted studies on individual hydrogen technologies including fuel cell vehicles, fuel cells and hydrogen power generation. However, an analysis on social infrastructure for hydrogen use from a macro viewpoint may be useful. Under such approach, this paper assumed a hydrogen town for the buildings sector for a cost and benefit analysis to extract problems and consider the feasibility of a hydrogen town.

If the ceiling hydrogen price is defined as the level to represent the present value of zero for the net benefit from substituting hydrogen-based energy infrastructure (a hydrogen town) for power grid and city gas infrastructure for a conventional town, our analysis results indicate a ceiling price of 21 yen per Nm3 (normal cubic meter) on a terminal shipment basis or 29 yen/ Nm3 on a user basis. This means that it is difficult to establish economic rationality for a hydrogen town at present,

while an estimate points out that hydrogen made from lignite in Australia could be imported into Japan at a CIF price of 30 yen/ Nm3.

However, there is a conceivable scenario in which fossil fuel prices will increase sharply, with Japan required to substantially reduce carbon dioxide emissions (under high carbon prices), while hydrogen technology development will make great progress to substantially cut hydrogen costs. In such case, the economy of a hydrogen town may improve substantially. Paying attention not only to imported hydrogen but also to a diversity of other hydrogen sources, we can conceive a scheme to reduce hydrogen distribution costs by producing hydrogen from regional energy resources for supply to regional hydrogen towns.

Hydrogen towns may also have social and economic spillover effects. Matters of concern to rural and suburban cities include the aging of urban infrastructure built in the high economic growth period, declining regional industries, and falling birthrates and aging population. Such cities could introduce hydrogen towns consuming locally produced hydrogen to create new local industries and jobs and vitalize regional economies. A hydrogen town scheme could provide clues as to rural cities' town building. Falling birthrates and aging population, industrial hollowing-out and regional revitalization and other challenges are not only faced by Japan but also by other developed countries mainly in Europe. By taking advantage of hydrogen to realize regional economies, Japan could provide a precedent for these countries. The precedent may also have useful implications for the environmental friendliness and sustainability of urban or regional development in emerging countries that will develop infrastructure from now on.

DEVELOPMENTS IN NUCLEAR POWER

近期報導：核電的發展

By Tomoko Murakami

On May 22, Kansai Electric's Takahama Unit 4 started operation, bringing the number of power plants permitted to operate under the new regulation standards to four. On May 24, Kansai Electric's Ohi Units 3 and 4 obtained a license, and 12 plants have now completed the safety assessment, including the three units that have been licensed to extend their operation. This number, however, is just under 30% of Japan's 42 existing plants, and is not high considering that five years have passed since the new regulatory standards came into effect. The review of construction plans and operation manuals remains extremely time-consuming, and the plants are unlikely to be restarted any faster.

In a referendum on "Energy Strategy 2050" held in Switzerland on May 21, a majority (approximately 58%) of the population voted for the revised Energy Act that promotes the nuclear-free policy, renewable energies, and energy efficiency. However, it must be noted that Switzerland decided to accept the nuclear-free policy as a result of opting for combining various renewable energies and energy efficiency measures to secure a stable supply of energy, unlike in Germany where safety concerns were the reason for abandoning nuclear power. In the wake of the referendum, an energy company Axpo, which considers that Beznau Unit 1, which started in 1969, is fit to operate until around 2030, argued that issues such as rising electricity costs due to soaring renewable capacities and

the market design to achieve decarbonization without compromising energy security have not been fully debated, and that "a proposal for resolving the market distortion will be put forward promptly." The future of Switzerland's nuclear power, which has one of the highest capacity factors in the world and is competitive in the market, is uncertain.

After being elected as the 19th president of the Republic of Korea on May 9, President Moon Jae-in is yet to announce a definite direction for the energy policy. On May 25, Korea Hydro & Nuclear Power (KHNP) announced that it was temporarily suspending design work on the new Hanul Units 3 and 4, which were due to start construction in May, until the new administration has fixed its policy on nuclear new builds. KHNP explained that the reason for the suspension is "to minimize the various impacts of the unknown policy on the new Hanul Units 3 and 4," emphasizing that the suspension is only partial and that work for licensing is continuing. The direction of nuclear new builds must be monitored in light of the revision of South Korea's strategic energy plan scheduled for 2018.

While its cost-competitiveness and social acceptance are weakening in many developed countries, nuclear power is still a promising base source of electricity in some developing countries. On May 17, China National Nuclear Corporation (CNNC) reached an agreement with Argentina's state-run nuclear power company Nucleoeléctrica Argentina S.A. concerning the construction of the country's fourth nuclear power plant Atucha Unit 3, and a fifth plant, which will be a Hualong-1 of China. It may be more important for the nuclear industries and governments of Japan and the West to recognize the fact that even a country that has traditionally adopted the technologies of developed countries, such as Siemens (present Areva) and Atomic Energy of Canada Limited, is switching to China for its next plants, and to analyze why this is happening, rather than just emphasizing the highest levels of reactor safety in the world in their nuclear export strategy.

HOW DO YOU COMBAT HIV RISK AMONG INTRAVENOUS DRUG USERS?

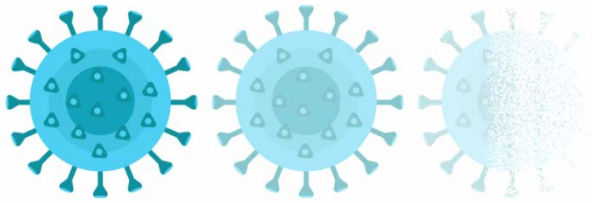
如何與靜脈注射用藥者感染 HIV 之風險對抗？

By Nicole Feldman

With the abuse of opioids on the rise in the United States, Stanford University researchers are concerned that increased HIV transmission from shared needles won't be far behind.

"There's an opioid epidemic in our country,

and there's a real public health crisis associated with injecting," said Cora Bernard, a graduate student in management science and engineering. "We think it's important to understand what investments give highest value because HIV prevention programs, and especially programs that reduce the prevalence of injection drug use, can have outsized positive impact on individuals, families and public safety."



Bernard is the lead author of a study on prevention programs that could head off a resurgence of HIV and perhaps decrease the effects of the opioid crisis. The study was published online May 24 in PLOS Medicine. The senior author is Margaret Brandeau, PhD, professor of management science and engineering.

In July 2016, Bernard and her co-authors published a different study examining pre-exposure prophylaxis, or PrEP, a pill that reduces a person's risk of infection when they come into contact with the HIV virus. The researchers found that PrEP was effective, but expensive.

The new study examines alternatives that also reduce the risk of HIV infection but are more cost-effective. They created a model to determine how many quality-adjusted life years — a metric that incorporates both life expectancy and quality of life — a person could gain from four HIV prevention methods, and what those years would cost.

" The dynamics of HIV prevention and treatment are complex," Brandeau said. "Our model allows us to evaluate the costs and effects of the interventions, singly and in combination, to determine what programs would be effective and cost-effective in preventing the spread of HIV among persons who inject drugs."

Prevention models studied

Of the prevention programs simulated in the model, the authors found that opioid agonist therapy, or OAT, was the most cost-effective. OAT replaces drugs like heroin with a prescription that provides similar effects under safer conditions. Methadone and buprenorphine maintenance therapies are the most common.

Needle-syringe exchange programs, in which people swap their dirty needles for clean ones, were the next most cost-effective option. This was followed by test-and-treat programs, which identify people with a high risk of contracting HIV, test them for the virus and treat them before the disease has much chance to spread — both within their own bodies and to others who are exposed.

The study estimated that PrEP can also successfully reduce HIV, but not in a cost-effective way. The authors write that the other three techniques could all cost less than $50,000 for each quality-adjusted life year

gained by individuals. PrEP would likely cost more than $600,000 per quality-adjusted life year.

The prevention programs were most effective when used in combination. The authors project that combining OAT and needle-syringe exchanges could avert up to 40,000 HIV infections over 20 years among people who inject drugs, not to mention preventing downstream sexual transmission of HIV to others in the population.

According to Bernard, one of the benefits of OAT in particular is that in addition to reducing the risk of HIV, it can also help people stop injecting drugs. The authors project that expanding OAT access could decrease the size of the injection population by up to 23 percent over 20 years for low-coverage expansions and up to 37 percent over 20 years for more extensive program expansions.

OAT found to be 'highest-value investment'

"We started out thinking about this as an HIV problem, but we realized that the majority of health benefit actually comes from reducing injection drug use and improving quality of life for drug users," said Bernard. "This is why we found OAT to be the highest-value investment."

Bernard and her co-authors believe that employing techniques like OAT could help reduce the effects of the opioid crisis.

"Our study aims to help policymakers and clinicians understand how a variety of interventions can help improve health outcomes and prevent HIV," said study co-author Douglas Owens, MD, professor of medicine and internist at the Veterans Affairs Palo Alto Health Care System. "We hope our analyses help show how to use limited resources efficiently to prevent the devastating consequences of substance use."

DID SOMETHING JOSTLE MY ARM? MY NEURONS NEED A MOMENT

誰撞了我的手嗎？我的神經元需要一點時間傳遞訊號

By Glen Martin

It happens all the time. You're carrying a full cup through a crowded room when someone unexpectedly jostles your arm. In a split second, your arm starts making the nuanced adjustments necessary to prevent a spill. No problem, right?

But as neuroscientists try to understand how the brain accomplishes this, they've noticed a mystery. The motor cortex, which helps control movement, registers the sensation of jostling almost immediately. But it pauses before ordering the muscles to react. Understanding why and how this occurs is critical to designing a

system to allow a person with paralysis to use their brain to control a prosthetic arm.

Now a team led by electrical engineer and neuroscientist Krishna Shenoy, director of Stanford's Neural Prosthetic Systems Lab, has solved the mystery of this brief pause between stimulus and response.

Writing in the journal Neuron, his team explains how cells in the motor cortex use this tiny interval of time to determine the appropriate muscular response.

"The brain has a mechanism to keep us from prematurely reacting when we are jostled," Shenoy said. "Now that we understand it we can design an electronic interface between the motor cortex and a prosthetic arm that works as nature intended."

This discovery has practical implications. Neuroengineers previously worried that when the brain is directly connected to a prosthesis, its earliest responses to perturbations would leak out and cause the arm to move erratically every time the user encountered something unexpected.

Brain-computer interface

The current findings build on Shenoy's long-term collaboration with Stanford neurosurgeon Jaimie Henderson. They are already doing clinical trials of a technology that allows people with paralysis to use their brains to "type" commands onto a virtual keyboard displayed on a computer screen.

Sergey Stavisky, a postdoctoral fellow in the Department of Neurosurgery and first author of the Neuron paper, explained how thought-controlled typing has worked in those clinical trials.

Several people with paralysis have been surgically implanted with one or more tiny silicon chips just beneath the skull. This chip is part of a system called a brain-computer interface, or BCI. Electrical leads on the chip pick up signals from neurons in the motor cortex that reveal what movement the person wants to make.

Developing a brain-controlled prosthetic limb is even more complicated. But some of the technology developed for the thought-controlled keypad has enabled the Stanford team to get a leg up on the arm challenge. In the new pre-clinical experiments they describe in Neuron, the Stanford researchers used the BCI to reverse-engineer the mechanism that enables the motor cortex to pause between stimulus – like when the arm is jostled – and response.

The experiments confirmed that during this delay the motor cortex, while recognizing the need to react, ever so briefly suppresses that urge while deciding what orders to send to the muscles.

"It's like having a scratch pad where you can first prepare a rough draft that no one else will see," Stavisky said.

This understanding is crucial to developing brain-controlled prosthetic arms. Shenoy said other researchers have already developed a prosthetic arm controlled by the brain, but they have not yet seen what happens when it encounters an unexpected perturbation.

"This problem has been worrisome," Shenoy said. "We knew that if we couldn't separate out the different neural patterns, we'd have trouble designing a brain-controlled prosthetic that works like a biological arm."

Shenoy said Stanford researchers want to design brain-controlled artificial limbs that don't overcompensate or overreact. The knowledge gained from the Neuron paper will feed into early-stage efforts to develop human clinical trials of prosthetic arms controlled through BCIs.

"Understanding how the brain responds when the arm is unexpectedly perturbed will be critical to making these efforts successful," Shenoy said.

Co-authors of the Neuron paper, "Motor Cortical Visuomotor Feedback Activity Is Initially Isolated from Downstream Targets in Output-Null Neural State Space Dimensions,"are Jonathan Kao, currently assistant professor at the University of California, Los Angeles, Department of Electrical Engineering, and Stephen Ryu, adjunct professor at Stanford's Department of Electrical Engineering. This work was supported by the National Science Foundation, the Christopher and Dana Reeve Foundation, the Burroughs Wellcome Fund, the DARPA REPAIR initiative and the National Institutes of Health.