WIV Newsletter
No.22 JUL 2018

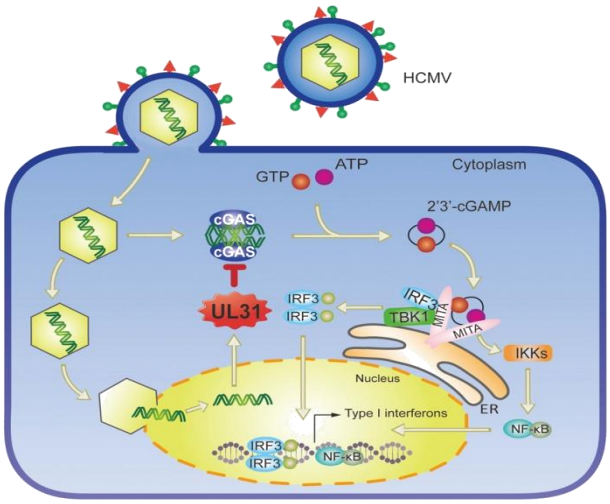
Scientists identify the human cytomegalovirus protein UL31 as an inhibitor of cGAS

The cytosolic DNA sensor cGAS recognizes viral DNA and synthesizes the second messenger cGAMP upon viral infection. Human cytomegalovirus (HCMV), a member of the betaherpesvirus family, is a typical dsDNA virus that encodes over 200 proteins. Similar to many other DNA viruses, HCMV infection induces activation of the cGAS-MITA signaling pathway.

Recently, it has been demonstrated that HCMV tegument protein UL82 contributes to HCMV immune evasion by inhibiting the cellular trafficking and activation of MITA/STING to evade antiviral immunity. However, whether the DNA sensor cGAS is targeted by HCMV proteins is largely unclear.

In a recent report, the research group led by Prof. WANG Yanyi in Wuhan Institute of Virology (WIV) of the Chinese Academy of Sciences (CAS), by cooperation with Prof. SHU Hongbing in Wuhan University and Prof. LUO Minhua in WIV, CAS, has identifed HCMV protein UL31 as an inhibitor of cGAS. UL31 interacts with cGAS, disassociates DNA from cGAS, and inhibits production of cGAMP, resulting in impaired antiviral immune responses.

In this study, the cytosolic DNA sensor cGAS recognizes viral DNA and synthesizes the second messenger cGAMP upon viral infection. cGAMP binds to the adaptor protein MITA/STING to activate downstream signaling events, leading to induction of type I interferons (IFNs) and antiviral effector genes. The scientists identify the human cytomegalovirus (HCMV) protein UL31 as an



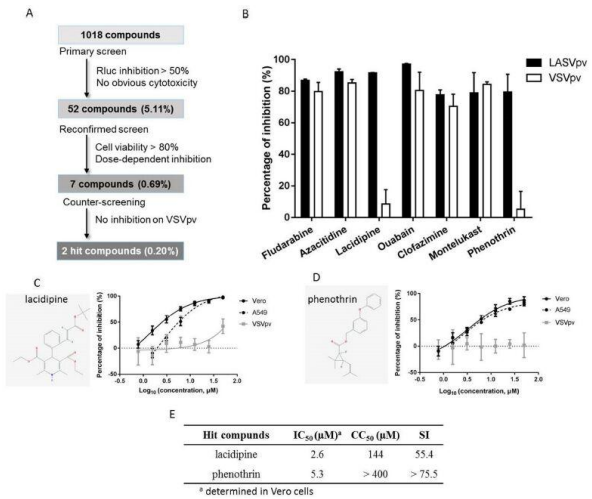
inhibitor of cGAS. UL31 interacts directly with cGAS and disassociates DNA from cGAS, thus inhibiting cGAS enzymatic functions and reducing cGAMP production. UL31 overexpression markedly reduces antiviral responses stimulated by cytosolic DNA, while knockdown or knockout of UL31 heightens HCMV-triggered induction of type I IFNs and downstream antiviral genes. Moreover, wild-type HCMV replicates more efficiently than UL31-deficient HCMV, a phenotype that is reversed in cGAS null cells.

These results highlight the importance of cGAS in the host response to HCMV as well as an important viral strategy to evade this innate immune sensor.

The results have been published in Cell Host & Microbe entitled "Human Cytomegalovirus Protein UL31 Inhibits DNA Sensing of cGAS to Mediate Immune Evasion".

Link: *https://www.sciencedirect.com/science/article/pii/S1931312818302610?dgcid=rss_sd_all*

Scientists show that lacidipine is a candidate for LASV therapy



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Hit compunds	IC_{50} (μM)[a]	CC_{50} (μM)	SI
lacidipine	2.6	144	55.4
phenothrin	5.3	> 400	> 75.5

[a] determined in Vero cells

Lassa virus (LASV) is an enveloped, negative-sense, bi-segmented RNA virus belonging to the Mammarenavirus genus (family Arenaviridae). To date, no vaccines or specific antiviral agents against LASV are available. Therapy strategies are limited to the administration of ribavirin in the early course of the illness.

To address this issue, the research group led by Prof. XIAO Gengfu in Wuhan Institute of Virology of the Chinese Academy of Sciences, shows that lacidipine is a candidate for LASV therapy, reinforcing the notion that the SSP-GP2 interface provides an entry-targeted platform for arenavirus inhibitors design.

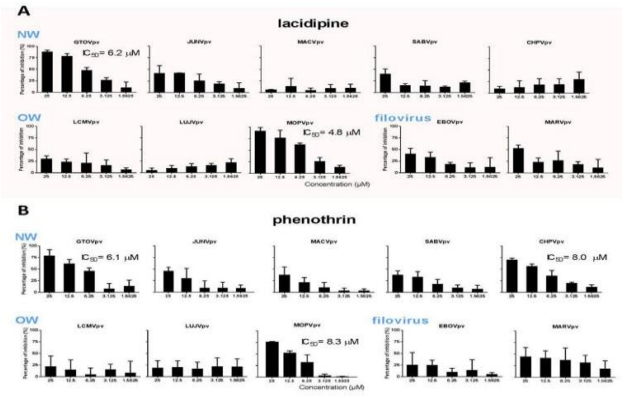
In this study, the scientists screened an FDA-approved drug library of 1018 compounds. The approved drugs have been intensively investigated for safety, pharmacokinetics, and targets; therefore, screening approved drugs for repurposing will increase the speed of discovery and development for treatment. Drugs targeting viral entry can block replication and spread at an early stage.

Since studies of LASV require BSL-4 equipment, the scientisrs utilized a LASV GPC pseudotype vesicular stomatitis virus (VSV) containing a Renilla luciferase (Rluc) reporter gene for high-throughput screening (HTS) of LASV entry inhibitors, which can be performed in a BSL-2 facility. After three rounds of screening, lacidipine and phenothrin were identified to be highly effective against LASV entry. The hit compounds identified in this study offer potential new therapies to treat arenavirus infections and disease.

The results have been published in Journal of Virology entitled "Screening and Identification of Lassa Virus Entry Inhibitors from an FDA-Approved Drugs Library".

This work was supported by the National Key Research and Development Program of China, the National Natural Sciences Foundation of China, the Open Research Fund Program of CAS Key Laboratory of Special Pathogens and Biosafety, Wuhan Institute of Virology, and the Open Research Fund Program of Wuhan National Bio-Safety Level 4 Lab of CAS, the Open Research Fund Program of the State Key Laboratory of Virology of China.

Link: *http://jvi.asm.org/content/early/2018/06/07/JVI.00954-18.abstract?papetoc*

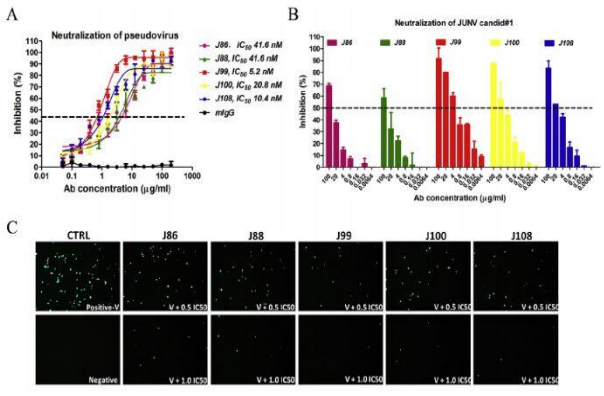


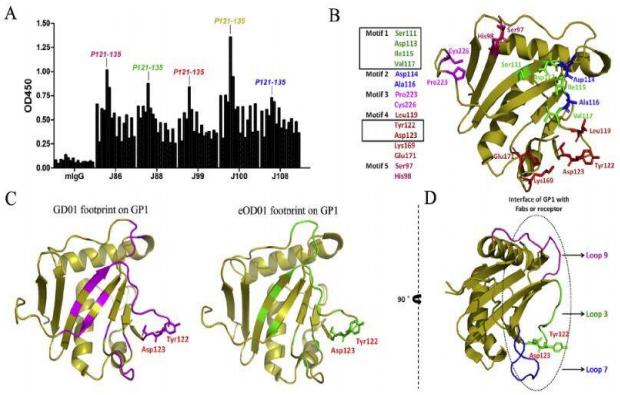
Scientists provide therapeutic candidates for protection against JUNV infection

Junin virus (JUNV) is the pathogen of Argentine haemorrhagic fever which results in high lethality, while there is limited therapeutics available.

In a recent study from research group led by Prof. XIAO Gengfu in Wuhan Institute of Virology of the Chinese Academy of Sciences, a series of mAbs were isolated based on a newly established strategy, and five were proven to effectively neutralize JUNV. Further research has characterized their abilities of binding conformational GPC and affinities for GP1. Epitope mapping revealed that these nAbs might interact with loop 3 of GP1, and their common binding sites were identified to be contained in those previously reported. This study proved the feasibility of producing nAbs against full-length arenavirus GPC via DNA immunization and identified potential therapeutic candidates for AHF.

Finally, five mAbs were found to effectively neutralize JUNV. Further research indicated that they were capable of binding conformational GPC and strongly binding glycoprotein 1 which is responsible for receptor recognition. Epitope mapping revealed that they targeted loop 3 of GP1, and Tyr122 and Asp123 in loop 3 were identified





as their common binding sites, which may account for their neutralizing activity.

Collectively, they have provided a new method for acquiring nAbs for pathogenic arenaviruses by screening antibodies against full-length GPC after immunization with DNA vectored with GPC gene. Moreover, five candidate nAbs were obtained, and their common epitopes were identified. Especially, loop 3 was hypothesized to be the most important domain for JUNV nAbs. This study provides therapeutic candidates against JUNV and clues to the discovery of new arenavirus vaccines and antibodies.

The results have been published in Antiviral Research entitled "Novel neutralizing monoclonal antibodies against Junin virus".

This study was funded by Natural Science Foundation of China and Open Research Fund Program of Wuhan National Bio-Safety Level 4 Lab of CAS, and supported by grants from the Chinese Academy of Sciences and the National Key Research and Development Program of China.

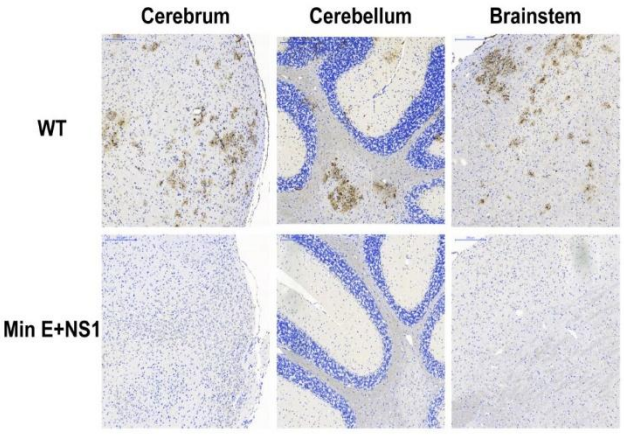
Link: *https://www.ncbi.nlm.nih.gov/pubmed/29870772*

ZIKV can be effectively attenuated by codon pair deoptimization

From June 2015, unprecedented epidemics of Zika virus (ZIKV) occur in the Americas, which cause the unexpected clinical symptoms including Guillain-Barre syndrome, microcephaly and other birth defects in human.

To date, there is no effective licensed vaccine or antiviral treatment against ZIKV infection, although several vaccine candidates have been described including formalin inactivated vaccines, live attenuated vaccines, genetic vaccines, and virus-like particle (VLP) vaccines. Therefore, new options for the development of ZIKV vaccine are needed.

In a recent report, the research group led by Prof. WANG Hanzhong in Wuhan Institute of Virology of the Chinese Academy of Sciences provided the first attenuated versions of ZIKV with two important genes (E and/or NS1) that were subjected to codon pair deoptimization. Compared to parental ZIKV, the codon pair-deoptimized ZIKVs were mammalian-attenuated, and preferred insect to mammalian Cells. Min E+NS1, the most restrictive variant, induced sterilizing immunity with a robust neutralizing antibody titer, and achieved complete protection against lethal challenge and vertical virus transmission during pregnancy.



In this study, the scientists describe the first large-scale recoding of ZIKV, a flavivirus that belongs to a large family of mosquito-borne human pathogens. Min E+NS1 displayed the potential to develop into a promising live-attenuated vaccine candidate.

Results from this study demonstrated the feasibility of rapid attenuation of ZIKV through the codon pair deoptimization strategy. The unparalleled advantage of the codon pair deoptimization strategy is that reversion to wild-type virulence is unlikely due to numerous synonymous substitutions without changing the amino acid sequence.

In summary, the codon pair deoptimization strategy would add the safety to the features of live attenuated viruses, which has a broad application in the development of vaccines for flavivirus and other important viruses.

The results have been published in Journal of Virology entitled "Zika Virus Attenuation by Codon Pair Deoptimization Induces Sterilizing Immunity in Mouse Models".

This work was supported by the National Key R&D Program of China, the National Natural Science Foundation of China (NSFC) and Youth Innovation Promotion Association of CAS.

Link: *http://jvi.asm.org/content/early/2018/06/14/JVI.00701-18.long*

Scientists suggest that doublecortin is modulated following infection of the brain by ZIKV

A Zika virus (ZIKV) outbreak has been ongoing in central and south America for the past 2 years, and has raised global concerns with regards to public health.

ZIKV has been shown to infect neural progenitor cells (NPCs) and inhibits cell proliferation, growth of neurospheres and brain organoids, suggesting that the neuropathology induced by ZIKV might be associated with NPC cell fate. However, the molecular mechanism(s) of ZIKV affecting neurogenesis still remains to be elucidated.

In a recent study, the research group led by Prof. LUO Minhua in Wuhan Institute of Virology of the Chinese Academy of Sciences utilized the primary human fetal NPC and the microinjection of fetal mouse brain to study the mechanisms of how ZIKV infection causes fetal brain development disorders.

The scientists found that NPCs were vulnerable to ZIKV infection, that multiple signaling pathways and cellular functions associated with neurogenesis were impaired by the infection, and that ZIKV infection downregulates DCX expression in NPC and mouse fetal brain, which further related to the decreased thickness of cortex layers.

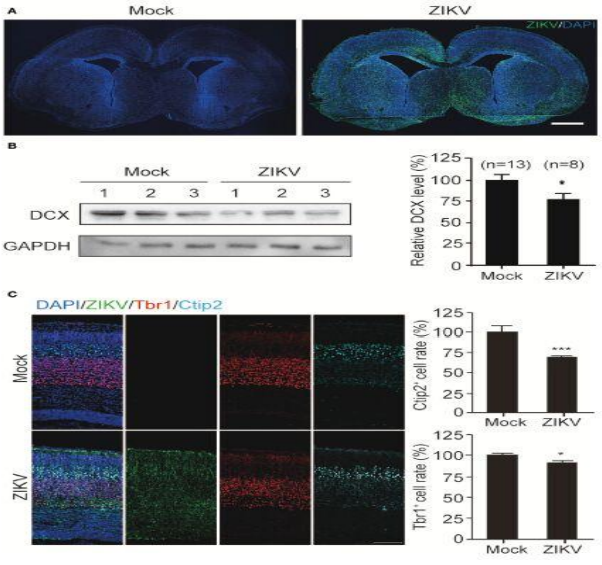
Further screening indicated that ZIKV NS4A and NS5 were related to the downregulation of doublecortin (DCX) in NPCs, which may contribute to the cortical structure defects caused by ZIKV.

In summary, their data extend the understanding of these two viral proteins in affecting cell fate of human NPCs. Further studies will be required to elucidate the specific means by which ZIKV NS4A, and NS5 influence the expression level of DCX.

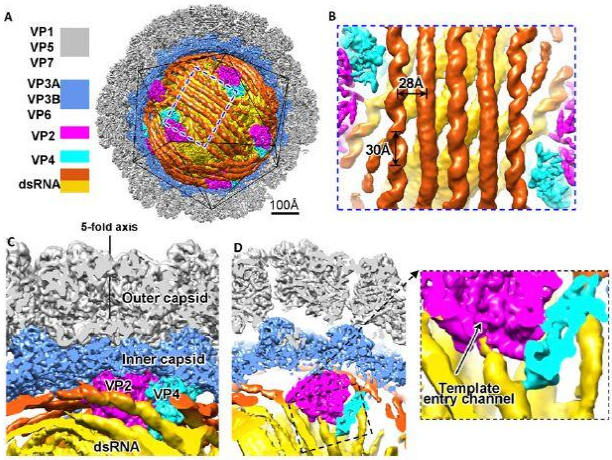
The results have been published in Frontiers in Microbiology entitled "Proteomic Analysis of Zika Virus Infected Primary Human Fetal Neural Progenitors Suggests a Role for Doublecortin in the Pathological Consequences of Infection in the Cortex".

The study was supported by the National Key Research and Development Program of China and the Major Program of Guangzhou healthcare collaborative innovation foundation, the Sino-Africa joint research center, Chinese Academy of Sciences and the National Nature Science Foundation of China.

Link: *https://www.frontiersin.org/articles/10.3389/fmicb.2018.01067/full*



Researchers present a structure of RNA polymerase complex and genome within a dsRNA virus



Double-stranded RNA (dsRNA) viruses infect hosts ranging from fungi to plants and to humans. Like most other dsRNA viruses, the aquareovirus RNA polymerase catalyzes the synthesis of RNA plus strands within the inner capsid, a process vital for the replication of virus progeny.

In a recent study, by cooperation with Tsinghua University, the research group led by Prof. FANF Qin in Wuhan Institute of Virology of the Chinese Academy of Sciences presented a near-atomic resolution structure of the RNA polymerase in complex with its cofactor protein and genomic RNA within the aquareovirus. Some asymmetric structures within the elaborate viral machine that have never been previously determined have been resolved in their structure, and key interactions among the polymerase, cofactor protein, and dsRNA have been revealed.

In this study, the scientists determined the structure of the RdRp protein VP2 in complex with its cofactor protein VP4 and genomic RNA within the double-layered aquareovirus capsid using cryoelectron microscopy (cryo-EM) at 200 kV and our symmetry-mismatch reconstruction method.

Their structure shows that the VP2–VP4 complex is anchored at the capsid shell and interacts with genomic dsRNA and four of the five asymmetrically arranged N termini of capsid shell protein VP3A under the fivefold axis, implying roles for these N termini in virus assembly. In addition, some elements in the VP2, which is supposed to interact with template RNA and priming nucleoside triphosphate (NTP) during transcription, are flexible.

A loop, which is thought to separate RNA template and transcript, was observed to interact with an apical domain of the shell protein VP3A, suggesting that the conformational change of the apical domain upon virus transcription activation could regulate RdRp replication and transcription. A conserved NTP binding site was localized in the VP4 structure, and both VP4 N-terminal and C- terminal domains are interacting with the genomic RNA.

These findings provide insights into the mechanism underlying highly coordinated dsRNA virus transcription and assembly. The results have been publishedin PNAS entitl ed "Structure of RNA polymerase complex and genome within a dsRNA virus provides insights into the mechanisms of transcription and assembly".

The study was supported by the National Research and Development Program of China, the National Natural Science Foundation of China, and Natural Science Foundation of Hunan Province.

Link: *http://www.pnas.org/content/early/2018/06/21/1803885115*

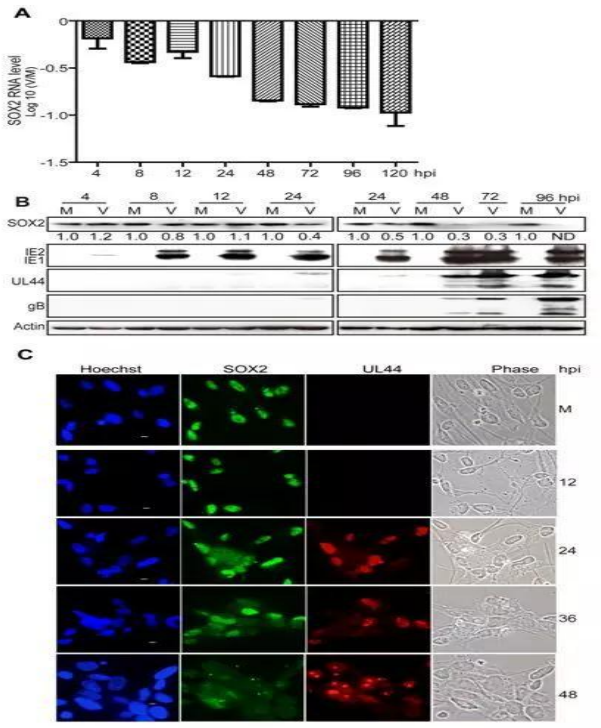
HCMV infection of NPCs results in the loss of the SOX2 protein

Congenital human cytomegalovirus (HCMV) infection is the leading cause of birth defects worldwide. Approximately 1% of live newborns are infected in utero with this virus. Recent advances in human neural progenitor cell (NPC) isolation and culture have provided an opportunity to study HCMV infection in a cell system relevant to fetal neuropathogenesis.

In a recent report, the research group led by Prof. LUO Minhua in Wuhan Institute of Virology of the Chinese Academy of Sciences investigated the effects of HCMV infection on SOX2 expression in human NPCs. They demonstrated that the HCMV 72-kDa immediate-early 1 (IE1) protein down regulates SOX2 transcription and mediates depletion of the SOX2 protein from HCMV-infected NPCs. IE1 exerts its effect on SOX2 expression by inactivating the upstream regulator STAT3.

In this study, the scientists reported that the HCMV proteins known as IE1 and IE2 target expression of human SOX2, a central pluripotency-associated transcription factor that governs neural progenitor cell (NPC) fate and is required for normal brain development. Both during HCMV infection and when expressed alone, IE1 causes the loss of SOX2 from NPCs. IE1 mediates SOX2 depletion by targeting STAT3, a critical upstream regulator of SOX2 expression.

In summary, this study initially links the interaction between IE1 and STAT3 to SOX2 depletion and thereby identifies a novel pathway predicted to contribute to developmental neuropathogenesis caused by congenital HCMV infection.



The results have been published in Journal of Virology entitled "Human Cytomegalovirus Immediate-Early 1 Protein Causes Loss of SOX2 from Neural Progenitor Cells by Trapping Unphosphorylated STAT3 in the Nucleus ".

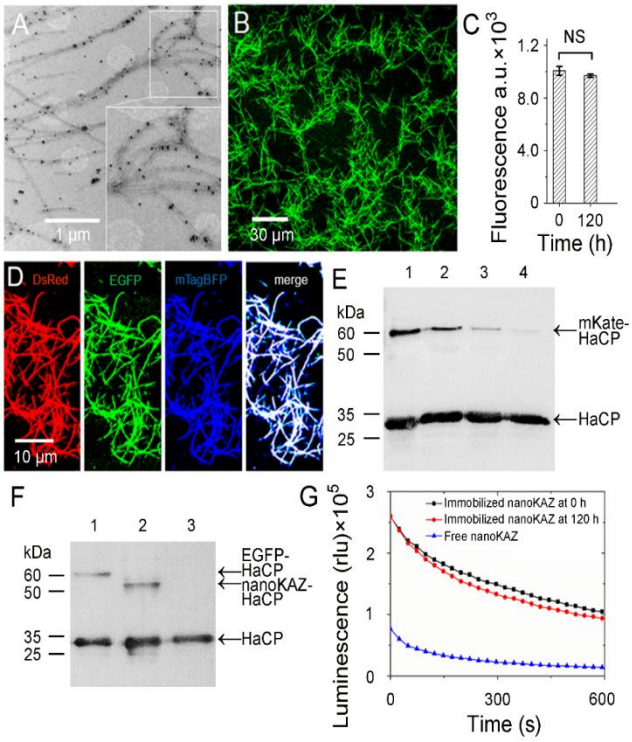
This work was supported by the Ministry of Science and Technology of China, the National Natural Science Foundation of China, the Sino-Africa Joint Research Centre, a seed grant from the University of Idaho, the Wellcome Trust Institutional Strategic Support Fund, the Medical Research Council and Tenovus Scotland, and the Deutsche Forschungsgemeinschaft.

Link: *http://jvi.asm.org/content/early/2018/06/21/JVI.00340-18.full.pdf+html?sid=cbbff88b-e8a3-4922-b6d0-3fe0b573c68a*

Scientists described a strategy for controllable assembly of flexible bio-nanotubes

Viruses with filamentous morphologies, such as tobacco mosaic virus (TMV) and M13 bacteriophage, have long been studied as multivalent nanoscaffolds for loading functional motifs. Structural assembly of the capsid proteins (CPs) of filamentous viruses often requires the presence of DNA or RNA molecules, which has limited their applications.

In a recent report, the research group led by Prof. CAO Sheng in Wuhan Institute of Virology of the Chinese Academy of Sciences described a strategy for controllable assembly of flexible bio-nanotubes consisting of Escherichia coli expressed CP of baculovirus Helicoverpa armigera nucleopolyhedrovirus (HearNPV) in vitro.



These protein-only nanotubes were studied as a new structural platform for high-density presentation of multiple active molecules on the exterior surface by direct fusion of the protein of interest to the N-terminus of HearNPV CP (HaCP). Structural characterization using cryoelectron microscopy demonstrated that the HaCP could assemble into two closely related but structurally distinct tube types, suggesting the tunable HaCP interaction network is the major contributor to the flexibility of HaCP nanotubes.

Their flexible nanotubes could tolerate larger molecular modifications compared with TMV-based templates and could be used as promising candidates for versatile molecular loading applications.

The results have been published in ACS Applied Materials & Interfaces entitled "Controllable Assembly of Flexible Protein Nanotubes for Loading Multifunctional Modules".

This work was supported by the National Natural Science Foundation of China and Chinese Academy of Sciences.

Link: *https://pubs.acs.org/doi/10.1021/acsami.8b07611*

Zeng Yixin visited Wuhan Institute of Virology, CAS

On June 5, Zeng Yixin, the Vice-minister and member of the Party Leadership Group of the National Health Commission, and vice-director of the Central Health Care Council, visited Wuhan Institute of Virology (WIV), Chinese Academy of Sciences (CAS).

Zeng Yixin and his colleagues visited the Wuhan National Biosafety Level 4 Laboratory of CAS to learn more about the laboratory construction history, functional layout, and the establishment of its biosafety management system. He listened to Chen Xinwen, the Director General of WIV, about the Institute and the Mega-Science Biosafety Center.

Zeng Yixin fully affirmed the unremitting efforts and exploratory contributions made by WIV in the construction of high-level biosafety laboratory and biosafety research. He hoped that the institute would complete the signature of the three-party strategic cooperation agreement among CAS, the Hubei Provincial Government, and the National Health Committee as soon as possible.

He pointed out that the operation of high-level biosafety laboratory provides a good platform for China's biosafety research and creates a better space for the future development of the institute. WIV must seize this opportunity to further strengthen the discipline layout and facilities platform to build, integrate all resources, create favorable conditions, try every means to attract a large number of young researchers, build a vibrant, high-level scientific research team, and push the research work to a new level. This is the Institute's top priority for development. The CAS, the Hubei Provincial Government and the National Health Commission should fully support the development of the Institute.

Liu Yingzi, the Director of Health and Family Planning Commission of Hubei Province, participated in the visit, and was accompanied by leaders from the Wuhan Branch of CAS and WIV.

Cooperation

CAS President's International Fellowship Initiative (PIFI)

CAS offers a package of international fellowships, collectively called the PIFI program to support highly-qualified international scientists and postgraduate students to work and study at CAS institutions and strengthen their scientific collaboration with CAS researchers. The PIFI program is available for four categories of international researchers and students: distinguished scientists, visiting scientists, postdoctoral researchers and international PhD students.

For more details: http://english.cas.cn/cooperation/fellowships/201503/t20150313_145274.shtml

Science Tips

A new Ebola species has been found in bats in Sierra Leone

A new species of Ebola virus has been discovered in bats in Sierra Leone, the country's government announced July 26. Researchers looking to identify new viruses before the pathogens spill over into human populations found the new Ebola strain while sampling bats in the northern Bombali district. This is the sixth known species of the virus.

RNA analysis of the virus revealed that it is "definitely related to other Ebola viruses," says Tracey Goldstein, a pathologist at University of California, Davis, who is with the virus-hunting PREDICT project. "But [it] was quite different."

Goldstein and her colleagues confirmed that the Bombali virus can infect human cells, but they still don't know whether or not it can cause disease in people. "It has the machinery" to enter a human cell, she says, but that doesn't mean that it can make people sick.

Some species of Ebola, such as the Reston virus, can cause disease in nonhuman primates but do not sicken humans. Other species of the virus however, like the Zaire virus, have been responsible for widespread epidemics, including a recent outbreak in the Democratic Republic of Congo that killed 33 people (SN Online: 5/18/18) and an earlier one responsible for more than 11,000 deaths across West Africa (SN: 1/24/15, p.12).

Science Tips

"We don't really know where on the spectrum [the Bombali virus] stands," Goldstein says. PREDICT and its partners are continuing to study the virus, and are educating people in the Bombali region to stay away from bats. At this point, Goldstein says, "I don't think people should be alarmed."

Source: *Science News*

Express News

Virologica Sinica obtains its first impact factor of 2.357

On June 26, Clarivate Analytics issued the latest journal citation report (JCR2017). In that report, Virologica Sinica received its first impact factor of 2.357 and ranked 21st in the total 35 journals of Virology Category in the JCR, located in Q3.

Virologica Sinica was founded in 1986 and co-sponsored by Wuhan Institute of Virology, Chinese Academy of Sciences and the Chinese Society of Microbiology. Since its publication in English in 2007, it has been aiming to create international virology journals. By enhancing editorial planning, publishing high-level special issues, increasing coverage of new outbreaks of viruses, and charging free layout fees and free English polish for accepted papers, the journal has attracted high-quality manuscripts at home and abroad, and the academic level and international influence have been continuously improved.

By the end of June 2018, 703 English papers had been published online in Virologica Sinica, covering more than 2,000 authors from more than 500 research institutions in 50 countries and regions around the world.