WIV Newsletter
No.12 Sep 2016

2016 International Conferences Alerts << Wuhan Institute of Virology, CAS

>> The 7th International Symposium on Emerging Viral Diseases

The 7th ISEVD will be held on October 19 to 21 in Wuhan Institute of Virology (WIV), CAS. This symposium aims at sharing latest findings, engaging in stimulating discussions and establishing collaborations with leading fellow scientists on emerging viral diseases all over the world. It will focus on four topics: (1) virus discovery, epidemiology and evolution; (2) antiviral and vaccine; (3) virus-host interaction, and (4) viral replication.

Website: http://isevd2016.csp.escience.cn

>> Nature Conference: Viral Infection and Immune Response

The Nature Conference on Viral Infection and Immune Response (VIIR), jointly hosted by WIV, Nature Microbiology, Chinese Society for Immunology and Committee on Virology, Chinese Society for Microbiology, will be held on Oct 21-23 in Wuhan, China. This Conference will focus on 6 topics: epidemiology of emerging viral disease, persistent viral infection and immune dysregulation, viral pathogenesis, immune intervention and prevention of disease, innate antiviral immunity and induction of systemic adaptive immunity.

Websites:
http://www.nature.com/natureconferences/viir2016/index.html
http://viir2016.csp.escience.cn

>> The 4th International Symposium for Herpes Virus, Associated Diseases and Antiviral Development

On November 5 to 7, 2016, the 4th International Symposium for Herpes Virus, Associated Diseases and Antiviral Development will be held in Wuhan, China. The symposium will focus on the following themes: 1.the pathogenesis of herpes virus associated diseases; 2.the antiviral strategies in herpes virus associated diseases; 3.the function of herpes virus genes; 4.mechanisms of herpes virus persistence infection, latency, and reactivation; 5.immune escape and host antiviral immune response during herpes virus infection; 6.screening, development and application of antiviral drugs.

Contact: Ms. Jinyan Sun at sunjy@wh.iov.cn

In Vivo Targeting and Imaging of Atherosclerosis Using Multifunctional Virus-Like Particles of Simian Virus 40

Atherosclerosis is a leading cause of death globally. Targeted imaging and therapeutics are desirable for the detection and treatment of the disease.

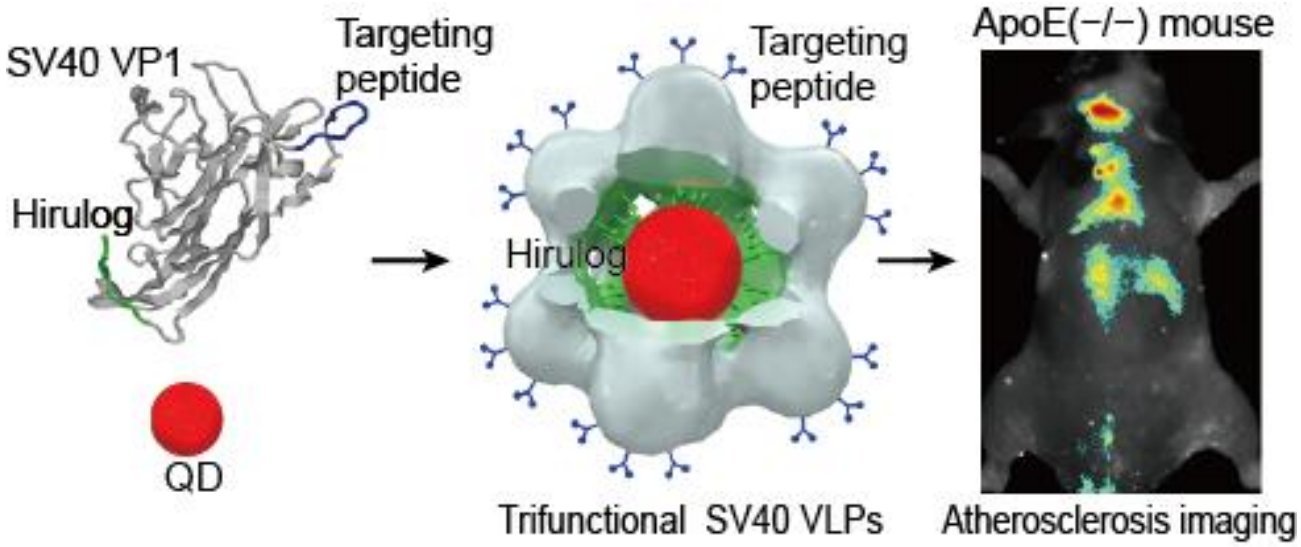
Recently, the research group led by Prof. Zongqiang Cui in WIV developed trifunctional Simian virus 40 (SV40)-based nanoparticles for in vivo targeting and imaging of atherosclerotic plaques. These novel trifunctional SV40-based nanoparticles encapsulate near-infrared quantum dots and bear a targeting element and a drug component.

Using trifunctional SV40-based nanoparticles, the scientists were able to noninvasively fluorescently image atherosclerotic plaques in live intact ApoE(−/−) mice. Near-infrared quantum dots encapsulated in the SV40 virus-like particles showed prominent optical properties for in vivo imaging. When targeting peptides for vascular cell adhesion molecule-1, macrophages, and fibrin were used, early, developmental, and late stages of atherosclerosis could be targeted and imaged in live intact ApoE(−/−) mice, respectively. Targeted SV40 virus-like particles also delivered an increased concentration of the anticoagulant drug Hirulog to atherosclerosis plaques.

This study provides novel SV40-based nanoparticles with multivalency and multifunctionality suitable for in vivo imaging, molecular targeting, and drug delivery in atherosclerosis.

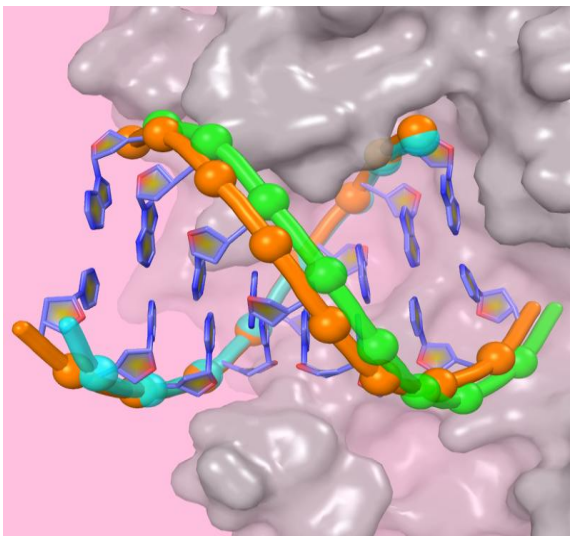
This paper was published online in Nano Letters. Their study was supported by grants from National Basic Research Program of China, the National Natural Science Foundation of China and Chinese Academy of Sciences.

Link: *http://pubsdc3.acs.org/doi/pdf/10.1021/acs.nanolett.6b02386*



Scientists in WIV reveal the asymmetric movement of the double-stranded RNA

RNA viruses encode a unique class of RNA-dependent RNA polymerases (RdRPs) to carry out their fully RNA-based genome replication and transcription. Although the chemical nature of nucleotide addition is essentially shared by all nucleic acid polymerases, the structural and mechanistic details taken by each polymerase class differ to various extents. The research group led by Prof. Peng Gong in WIV reports seven crystal structures of enterovirus 71 RdRP elongation complex at 2.5–2.8 Å resolution. In these structures the polymerases are poised at various distinct stages to reveal mechanistic details of initial NTP binding, key amino acid side-chain conformational switches during active site closure, and in particular the postcatalysis movement of the RNA duplex on the way to vacate the active site for the next nucleotide addition cycle.



Viral RNA-dependent RNA polymerases (RdRPs) play essential roles in viral genome replication and transcription. The research group previously reported several structural states of the poliovirus RdRP nucleotide addition cycle (NAC) that revealed a unique palm domain-based active site closure mechanism and proposed a six-state NAC model including a hypothetical state representing translocation intermediates. Using the RdRP from another human enterovirus, enterovirus 71, here they report seven RdRP elongation complex structures derived from a crystal lattice that allows three NAC events. These structures suggested a key order of events in initial NTP binding and NTP-induced active site closure and revealed a bona fide translocation intermediate featuring asymmetric movement of the template–product duplex. Their work provides essential missing links in understanding NTP recognition and translocation mechanisms in viral RdRPs and emphasizes the uniqueness of the viral RdRPs compared with other processive polymerases.

Link: *http://www.pnas.org/content/113/28/E4005.long*

Chinese Researchers Reveal Redox Sensor Protein Role in Pathogenic Mycobacteria

As one of the most successful intracellular pathogens, Mycobacterium tuberculosis (Mtb) causes 8 million cases of tuberculosis and 1.3 million deaths worldwide annually. During the course of infection, Mtb is exposed to diverse redox stresses that trigger metabolic and physiological changes.

Research Progress

However, it remained unclear how these stressors are sensed and relayed to the Mtb transcriptional apparatus. Researchers already knew that the ESX-1 secretion system encoding a type VII secretion system is unique to mycobacteria and is required for acute infection, while the DosRS regulon is required for long-term persistence in Mtb.

Furthermore, association of nitric oxide (NO) produced by host cells and upregulation of DosR as well as whiB6 has been documented, but how this happens remained to be elucidated.

New research carried out by scientists with the Center for Emerging Infectious Diseases, Wuhan Institute of Virology (WIV) of the Chinese Academy of Sciences, dissects the cellular role of WhiB6, one of the WhiB redox sensor family proteins, in virulence and intracellular survival of pathogenic mycobacteria.

Their study was published online on August 18 in Cell Reports.

"Using the M. marinum-zebrafish infection model, we provide compelling evidence showing that WhiB6 acts as a finely tuned regulator of the ESX-1 secretion system and DosR regulon with its Fe-S cluster in response to NO," said CHEN Zhenkang, first author of the paper.

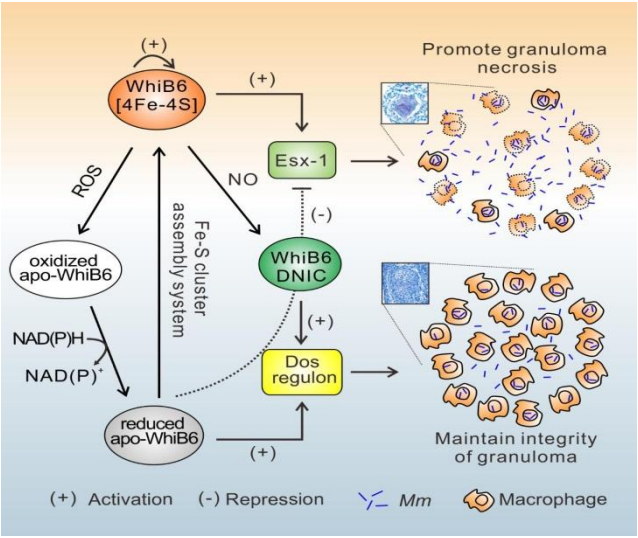
As Mtb infection worsens, infected macrophages activate additional macrophages and other immune cells to form a granuloma, which is an organized collection of macrophages composed of mononuclear phagocytes, dendritic cells, as well as T and B lymphocytes.

"Our study reveals that WhiB6 regulation has altered function due to change toward its Fe-S cluster, which enables mycobacteria to establish persistent infection and maintain integrity of the granulomas. We propose a model to explain how WhiB6 plays in different regulatory roles to modulate the development of granulomas," said Dr. CHEN Shiyun, a principal investigator and the corresponding author of the paper.

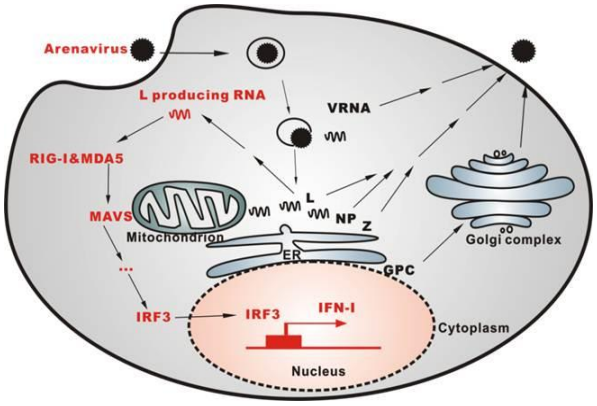
"Our work is of great interest not only to the specific field of mycobacteriology, but also to the broader readership interested in host-pathogen interaction and related mechanisms," he said.

The study, "Mycobacterial WhiB6 differentially regulates ESX-1 and the Dos regulon to modulate granuloma formation and virulence in zebrafish," was supported by grants from the CAS Key Program and National Natural Science Foundation of China (NSFC). Additional authors include Bridgette Cumming and Adrie Steyn from the KwaZulu-Natal Research Institute for Tuberculosis and HIV, South Africa.

Link: *http://www.cell.com/cell-reports/pdf/S2211-1247(16)31026-9.pdf*



WIV found the new mechanism that Arenaviridae affects the natural immune system



The Arenaviridae family includes several important human pathogens that can cause severe hemorrhagic fever and greatly threaten public health. As a major component of the innate immune system, the RLR/MAVS signaling pathway is involved in recognizing viral components and initiating antiviral activity. It has been reported that arenavirus infection can suppress the innate immune response, and arenavirus NP and Z proteins of pathogenic arenaviruses can disrupt RLR/MAVS signaling, thus inhibiting production of IFN-I. However, recent studies have shown elevated IFN-I levels in certain arenavirus-infected cells. The mechanism by which arenavirus infection induces IFN-I responses remains unclear.

In this study, the research group led by Prof. Gengfu Xiao in WIV determined that the Lp of Mopeia virus (MOPV), an Old World (OW) arenavirus, can activate the RLR/MAVS pathway and thus induce the production of IFN-I. This activation is associated with the RNA-dependent RNA polymerase activity of Lp. This study provides a foundation for further studies of interactions between arenaviruses and the innate immune system and the elucidation of arenavirus pathogenesis.

The scientists demonstrate for the first time that the Lp of MOPV, an OW arenavirus, can activate the RLR/MAVS signaling pathway and thus induce the production of IFN-I. Based on our results, we proposed that dynamic interactions exist among Lp-produced RNA, NP and the RLR/MAVS signaling pathway, and the outcome of these interactions may determine the final IFN-I response pattern: elevated or declined. Their study provided a possible explanation for how IFN-I can become activated during arenavirus infection and may help gain insights into the interactions that form between different arenavirus components and the innate immune system.

Link: *http://www.ncbi.nlm.nih.gov/pubmed/27605671*

WIV Researchers developed a three-fragment fluorescence complementation system

Many cellular processes are governed by molecular machineries that involve multiple protein interactions. However, visualizing and identifying multiprotein complexes such as ternary complexes inside cells is always challenging, particularly in the subdiffraction cellular space.

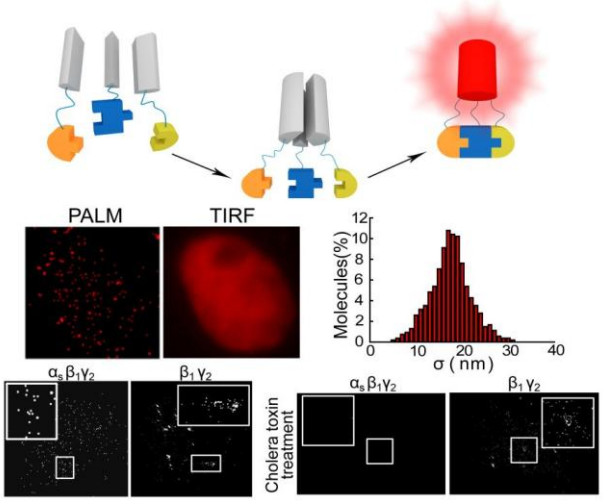
The research group led by Prof. Zongqiang Cui in WIV developed a three-fragment fluorescence complementation system (TFFC) based on the splitting of a photoactivatable

Research Progress

Fluorescent complementation system (TFFC) based on the splitting of a photoactivatable fluorescent protein, mIrisFP, for the imaging of ternary complexes inside living cells. Using a combination of TFFC and photoactivated localization microscopy (PALM), namely, the TFFC-PALM technique, we are able to identify the multi-interaction of a ternary complex with nanometer-level spatial resolution and single-molecule sensitivity.

The TFFC-PALM system has been further applied to the analysis of the Gs ternary complex, which is composed of αs, β1, and γ2 subunits, providing further insights into the subcellular localization and function of G protein subunits at the single-molecule level. The TFFC-PALM represents a valuable method for the visualization and identification of ternary complexes inside cells at the nanometer scale.

Link: *http://pubs.acs.org/doi/abs/10.1021/acsnano.6b03543*

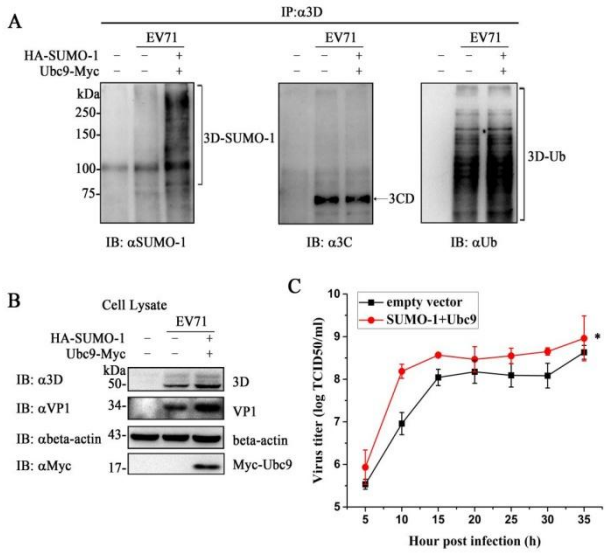


SUMO Modification Stabilizes Enterovirus 71 Polymerase 3D to Facilitate Viral Replication

Accumulating evidences suggest that viruses hijack cellular proteins to circumvent the host immune system. Ubiquitination and SUMOylation are extensively studied post-translational modifications (PTMs) that play critical roles in diverse biological processes. Crosstalk between ubiquitination and SUMOylation of both host and viral proteins has been reported to result in distinct functional conses1quences. Enterovirus 71 (EV71), an RNA virus belonging to Picornaviridae family, is a common cause of hand, foot and mouth disease. Little is known concerning how host PTM systems interact with enteroviruses.

Under this circumstance, Prof. Hanzhong Wang and his research group in WIV demonstrated that the 3D protein, an RNA-dependent RNA polymerase (RdRp) of EV71, is modified by small ubiquitin-like modifier-1 both during infection and in vitro. Residues K159 and L150/D151/L152 were responsible for 3D SUMOylation determined by bioinformatic prediction combined with site-directed mutagenesis. And primer-dependent polymerase assays indicated that mutation of SUMOylation sites impaired 3D polymerase activity and virus replication. Moreover, 3D is ubiquitinated in a SUMO-dependent manner, and SUMOylation is crucial for 3D stability which may be due to the interplay between the two PTMs. Of importance, increasing the

Research Progress



level of SUMO-1 in EV71-infected cells augmented the SUMOylation and ubiquitination level of 3D, leading to enhanced replication of EV71. These results together suggested that SUMO and ubiquitin cooperatively regulated EV71 infection either by SUMO-ubiquitin hybrid chains or by ubiquitin conjugating to the exposed lysine residue through SUMOylation. Their study provides a new insight into how a virus utilizes cellular pathways to facilitate its replication.

Link: *http://jvi.asm.org/content/early/2016/09/08/JVI.01756-16.abstract*

Cooperation

Prof. Zhihong Hu is elected as Vice President of the Society for Invertebrate Pathology

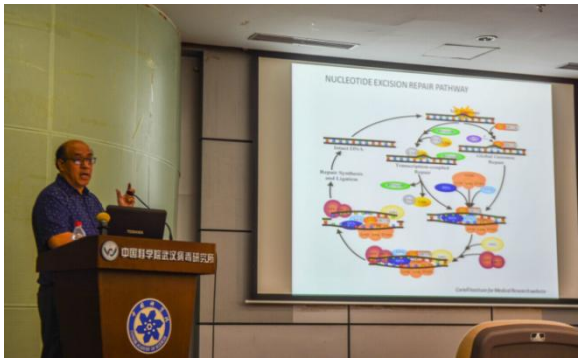
In the 49th Annual Meeting of the Society for Invertebrate Pathology (SIP) held on 24-28th of July 2016 in Tours, Loire Valley, France, Prof. Zhihong Hu in WIV is notified to be elected as Vice President of the Society for the term July 2016 to August 2018. This is the first time for the scientist outside the U.S. and Europe to assume an important leading position in SIP.

The Society for Invertebrate Pathology was founded in 1967 as an interdisciplinary scientific society that would draw together members from diverse scientific backgrounds under the unified discipline of invertebrate pathology. Now SIP sets up 7 divisions: Bacteria, DBI, Fungi, Microbial Control, Microsporidia, Nematodes and Virus. The objectives as defined in the Society's constitution are: i) Promotion of scientific knowledge of pathology of invertebrate animals and of related subjects through discussions, reports and publications. ii) Stimulation of scientific investigations and their applications. iii) Planning, organization and administration of projects for the advancement of scientific knowledge in invertebrate pathology. iv) Improvement of education and of professional qualifications in invertebrate pathology. v) Promotion of international cooperation in achieving the above objectives.

The election of Prof. Hu does not only represent the international positive attitude towards her outstanding academic achievement, but also is the symbol of the climbing influence from China in the field of invertebrate pathology. Prof. Hu was one of the members of the council in that society. According to the regulation, she will be promoted as the President of SIP from 2018 to 2020.

Speakers on "Ge Hong Colloquium"

On August 8, Dr. Xia Zhou, the assistant professor in Department of Internal Medicine at University of Kansas Medical Center, paid a visit to WIV and gave an excellent talk on “Epigenetic Regulators Promote Renal Cyst Growth in Autosomal Dominant Polycystic Kidney Disease”, which suggested epigenetic regulators may be modifiers of autosomal dominant polycystic kidney disease.



Dr. Fan Li, the associate professor in Department of Biochemistry at University of California, visited WIV on August 30. On the Colloquium, he reported his recent research effort to address fundamental questions in DNA repair and recombination using a multi-disciplinary approach including X-ray crystallography, molecular biology, and biochemistry.

2017 CAS-TWAS President’s Fellowship Programme for Doctoral Candidates

According to an agreement between CAS and The World Academy of Sciences (TWAS) for the advancement of science in developing countries, up to 200 students/scholars from all over the world will be sponsored to study in China for doctoral degrees for up to 4 years. Under this programme, students who are non-Chinese citizens have the opportunity to pursue doctoral degrees at the University of Chinese Academy of Sciences (UCAS), the University of Science and Technology of China (USTC) or Institutes of CAS around China. Here WIV is calling for application to study in our institute under the programme.

Deadline for submitting applications:
31 MARCH 2017

Where to enquire and submit application:
Ms.Pei Pingping
The Graduate Office
Email: yjs@wh.iov.cn

Innovation Flies Dreams and Technology Leads Future

— Active Participation of WIV on National Science Popularization Day

The kick-off ceremony and home field activity of 2016 National Science Popularization Day in Hubei was jointly hosted by Hubei Association for Science and Technology, Science and Technology Department of Hubei Province, Hubei Provincial Department of Education and Wuhan Branch of Chinese Academy of Science at the Wuhan Branch of Chinese Academy of Science on September 14th afternoon. Responding positively, Wuhan Institute of Virology went all out to organize and participate in the activity.

This year's National Science Popularization Day was themed on "Innovation Flys Dreams and Technology Leads Future". All relevant activities were carried out around aspects such as vigorously spreading the idea of development, advocating innovation, creation and entrepreneurship, promoting understanding of high-tech among public, introducing scientific lifestyle. In the science popularization activity, Wuhan

Institute of Virology demonstrated the relationship between virus and human beings – friendly and hostile, harmonious while competitive – through various posters of science popularization, Virus and Human Health booklet, 3D models and display boards. Through such demonstration, the unremitting efforts made and the scientific spirit of scientists and researchers generation after generation in fighting against plagues or epidemics threatening humankind were also fully exhibited.

In front of the exhibition hall of Wuhan Institute of Virology, volunteers introduced the popularization work of science of Wuhan Institute of Virology, especially the new media construction for this end, which has been praised by Guo Shenglian, the vice governor of Hubei Province. He encouraged the Institute to keep focusing on the key issues concerning human's existence, including biosafety, emerging infectious diseases, and to further carry out popularization work about knowledge of virus and health.

Tan Tieniu's Visit to Wuhan Institute of Virology

The vice president of Chinese Academy of Sciences Tan Tieniu visited Wuhan Institute of Virology on August 22th afternoon and a symposium has been held.

Tan firstly visited Wuhan P4 laboratory. In the laboratory, he asked the details of the laboratory's functional layout, construction process, commissioning and operation situations, biosafety management and so on. He also communicated with the working team which is responsible for the laboratory's operation and maintenance. A symposium was held later. In the symposium, Chen Xinwen, director of Wuhan Institute of Virology reported the general situation of technical innovation, focusing on the Institute's key programs such as "One-Three-Five Plan" (one research and development orientation, three breakthroughs and five cultivating areas) and "Being the First to Act"; Yuan Zhiming, director of Wuhan Branch of Chinese Academy of Sciences, introduced the Sino-France cooperation background and summarized the achievements that have already been made through the Sino-France cooperation in areas such as science and technology, the construction of biosafety system and personnel training.

Tan highly praised the work done by Wuhan Institute of Virology. "You never know how difficult it is till you try", Tan said. "Wuhan P4 laboratory is a remarkable achievement of Sino-France cooperation. It is a platform that provides conditions for collaborative innovation at home and abroad, and is of vital strategic importance for China as a country to safeguard its national security. Wuhan Institute of Virology, constructed on the basis of P4 laboratory, has always been working according to the national strategic demands and has been playing a positive role in areas such as prevention and control of emerging infectious diseases and dealing with national public health emergencies.