Seeking protection for all

By promoting basic life sciences research, a medical biology institute in China has accelerated the development and clinical use of vaccines, offering PROTECTION AGAINST DISEASES.

Qihan Li, director of IMBCAMS, leads a strong team.

Gene editing technologies for establishing animal disease models

Vaccine development has served a vital role in the fight against infectious diseases for more than 200 years. While every disease, whether polio or influenza, presents different challenges, the process of vaccine development begins with basic science. As researchers deepen their mechanistic understanding of the immune response, new avenues for vaccine development emerge.

At the Institute of Medical Biology, Chinese Academy of Medical Sciences (IMBCAMS), researchers have been studying the balance between immune activation and immune regulation, and integrating the basic medical research with vaccine R&D and production for decades, according to Qihan Li, director of IMBCAMS. A look at its past and present projects demonstrates how IMBCAMS drives the development of the health industry in China.

A history of fighting diseases

IMBCAMS was established in 1958, and researchers there developed an attenuated poliomyelitis vaccine shortly after. It was effective in slowing the spread of polio in China.

However, the attenuated vaccine contained a weakened form of the pathogens, which had the potential to become a source of polio reemergence. To eradicate the disease in China, IMBCAMS researchers set out to develop an inactivated polio vaccine (IPV) that contains no live viruses, but can still generate an immune response.

IPV is typically produced from wild-type poliovirus (WPV) strains, which has very stringent manufacturing controls. Given the risks of large quantities of WPV, the IMBCAMS team aimed for a safer alternative. They found that IPV prepared from attenuated Sabin strains can generate the same level of immune response and protective efficacy as that from wild strains. They also explored the safety and immunogenicity of this Sabin-IPV (sIPV), providing guidance for its clinical use.

In 2015, the sIPV developed by IMBCAMS gained new drug application approval, offering a more affordable and safer way to produce IPV.

IMBCAMS also developed the live-attenuated vaccine for hepatitis A virus (HAV) in 1992, responding to a major outbreak in China in 1988. Using the marmoset as the animal model, researchers established HAV attenuation/virulence indicators, which provided criteria for evaluating the attenuation and protection efficacy of vaccine strains. They also selected an HAV strain with good immunogenicity, strong proliferation capacity, and high stability for vaccine production. Capable of promoting immunity without inducing the disease, this vaccine, primarily used in China, achieves ideal efficacy with a one-dose regimen.

Designated as a World Health Organization Collaborative Research Center on Enterovirus, IMBCAMS is also known for its launch of one of the world's first inactivated enterovirus-71 (EV71) vaccine for hand, foot and mouth disease (HFMD). Characterized by sores in the mouth and rashes on the hands and feet, the HFMD virus may lead to fatal cardiopulmonary failure in severe cases. When China first experienced an outbreak, IMBCAMS quickly responded by isolating the major pathogen, EV71. Via screening, they identified the vaccine strain suitable for large-scale production.

Researchers also developed rhesus monkey models capable of inducing the clinical symptoms for studying HFMD infection, its pathological and immunological mechanisms, and for evaluating vaccine efficacy. In comparing responses to viral infection and vaccine antigen in children and monkeys, researchers observed a similar increase in neutralizing antibodies, and comparable T cell immune responses, indicating positive prospects for clinical translation. Based on the results from these preclinical studies, clinical trials were performed, and showed good immune persistence, immune memory effect, and effective protection of the vaccine.

Vaccine purification process

Viral cultivation preparation

The latest disease control effort by IMBCAMS is focused on the COVID-19 pandemic. Based on the primate model created at the National High-level Biosafety Primate Research Center, an affiliate of IMBCAMS, researchers have explored the proliferation and inactivation mechanism of the SARS-CoV-2 virus, and developed an inactivated vaccine candidate. They have completed the preclinical evaluation for safety and efficacy, and the vaccine candidate has completed phase I/II clinical trial.

Emphasizing the fundamentals

IMBCAMS's success stems from its strength in basic and clinical science."We focus on both the immunological protection mechanism and the clinical research of vaccines," Li says.

Consider the studies of the EV71 vaccine. By studying the interaction between virus and host's immune cells, and exploring T cell responses and tissue expression characteristics of key inflammatory factors, IMBCAMS researchers revealed the immune-response characteristics of EV71 infection and the possible pathogenesis of severe cases. This knowledge provided the theoretical immunological basis for successful development of the vaccine.

In evaluating the vaccine, IMBCAMS researchers analysed the gene function of peripheral blood monocytes through gene expression profiling technology. They showed that the inactivated EV71 vaccine can mobilize related immune processes without causing significant inflammation, providing evidence of the vaccine's safety.

The same logic applies to existing vaccines, some of which might have been developed with production methods that are now outdated, or with incomplete understanding of mechanisms of action. At IMBCAMS, researchers targeted existing mumps, rabies, and meningitis vaccines and improved their efficacy and safety.

Addressing new challenges

Of the greatest challenges faced by vaccine developers, one is simply time. The faster vaccine development can occur, without sacrificing safety and efficacy, the more quickly public health officials can stamp out emerging infectious diseases. Few examples are more illustrative than influenza. To accelerate the process of influenza vaccine development, IMBCAMS researchers, based on prior knowledge of the virus, applied a reverse genetic technology, which uses known viral genetic sequences to create a weakened virus. This allowed for rapid generation of strains, enabling quick response to influenza outbreaks, and to diseases like dengue fever, Zika, and more.

IMBCAMS researchers have also used the reverse vaccinology technique to identify effective antigens and transform vaccine strains for pathogens that may have unique life cycles and infection characteristics, or are difficult to amplify in large quantities.

Technologies they used to address the challenge also include gene editing, recombinant design, bioinformatics screening, bionic nanotechnology, and high-density fermentation preparation.

Another emerging need is developing universal vaccines or multivalent vaccines for diseases caused by various types of pathogens, or to address frequent pathogen mutations. IMBCAMS researchers have developed technologies for analysing and identifying conserved antigen epitopes, enabling efficient antigen design and preparation. Utilizing innate immune response and memory, they are also exploring new strategies for developing universal vaccines that induce effective protection against multiple types of pathogens.

Many researchers believe vaccines will move from preventing infectious diseases to becoming therapeutic interventions for non-communicable diseases, such as asthma, hypertension, autoimmune diseases, and cancer, and IMBCAMS is preparing for this future. It is focusing on bioinformatics screening and recombinant preparation of antigens, efficient delivery with nano systems, regulation of immune response and of the immunity environment. That basic understanding, translated for the clinic, could fuel a new generation vaccines.

"As a comprehensive research institution and production base for vaccines, we will continue safeguard the health of people in China and beyond," Li says. ■

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