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National Institutes of Biomedical Innovation, Health and Nutrition
Sumitomo Pharma Co., Ltd.

Elucidation of the Mode of Action of Novel Universal Influenza Vaccine Candidates

The National Institutes of Biomedical Innovation, Health and Nutrition (Ibaraki, Osaka, Japan; President: Yusuke Nakamura; hereafter, "NIBIOHN") and Sumitomo Pharma Co., Ltd. (Head Office: Osaka, Japan; Representative Director, President and CEO: Hiroshi Nomura; hereafter, "Sumitomo Pharma") announced today that the results of the latest successful study conducted by a joint research group of the NIBIOHN, Sumitomo Pharma, and the National Institute of Infectious Diseases (Shinjuku, Tokyo, Japan; Director-General: Takaji Wakita) to develop "universal influenza vaccines" that provide protection against a broad range of influenza viruses. The group, for the first time, has demonstrated that their novel universal influenza vaccine candidate formulations adjuvanted with "DSP-0546LP", a toll-like receptor 7 (TLR7) agonist, provide a strong protection against heterologous strains (cross-protection), elucidated the mode of action of the formulations, and indicated the significance of the TLR7 adjuvant "DSP-0546LP."

The results of this study were published online in the international academic journal *Vaccine* on June 15, 2023.

1. Background

Conventional influenza vaccines lose effectiveness due to viral mutations, making it necessary to produce and inoculate a vaccine to immunize against strains predicted to circulate each year. They may also not respond well to emerging strains of influenza. Therefore, there is a need to develop and commercialize "a universal influenza vaccine" that improves the breadth and durability of protection against seasonal influenza viruses and is effective against novel and potentially pandemic strains.

2. Study Results

The joint research group is developing candidate vaccine formulations targeting the post-fusion hemagglutinin (HA) antigen that are adjuvanted with DSP-0546LP (hereafter, "DSP-0546LP-adjuvanted formulations"). These formulations are expected to be effective against

a broad range of influenza viruses. In this study, the researchers investigated the cross-protection and detailed mode of action of DSP-0546LP-adjuvanted formulations in mouse models of influenza infection (Fig. 1).

Experiments in mice immunized with the post-fusion HA form antigen with or without the adjuvant to evaluate immune responses provided the following findings:

i) DSP-0546LP-adjuvanted formulations induce cross-reactive antibodies more efficiently than non-adjuvanted formulations do.
ii) Adjuvanting with DSP-0546LP strongly induces Th1-polarized immune responses, as demonstrated by the production of antigen-specific interferon (IFN)-γ and IgG2c antibodies.
iii) DSP-0546LP enhances antibody-dependent cellular cytotoxicity (ADCC) activity against influenza strains antigenically different from those used in vaccine formulations.
iv) Antibodies induced by DSP-0546LP-adjuvanted formulations do not show significant neutralizing activity against heterologous influenza viruses.

Thereafter, the group evaluated the cross-protection of DSP-0546LP-adjuvanted formulations in a mouse challenge study with influenza viruses antigenically different from those used in vaccine formulations. The post-fusion HA antigen formulations adjuvanted with DSP-0546LP, not the non-adjuvanted formulations, provided significant cross-protection.

The above results indicate that the DSP-0546LP adjuvant plays an important role in inducing functional antibodies. The findings suggest that the novel universal influenza vaccine candidate formulations developed by the group may provide potent cross-protection by enhancing ADCC activity through the elicitation of Th1-mediated immune responses, not by inducing neutralizing antibodies against heterologous strains.

3. Future Development

This study provided the non-clinical proof-of-concept supporting the development of DSP-0546LP-adjuvanted formulations (Fig. 2), which represents a major step towards the clinical application of “a universal influenza vaccine.” The group will continue to conduct research and development with a view to an early practical application.

4. Research Structure and Supports

This study was supported by grants from the Cyclic Innovation for Clinical Empowerment (CiCLE) and the Research Program on Emerging and Re-emerging Infectious Diseases of the Japan Agency for Medical Research and Development (AMED). The NIBIOHN and Sumitomo Pharma have been conducting a joint study titled “Research and Development of Universal Influenza Vaccines,” covered by the AMED’s CiCLE funding.

5. Glossary

Post-fusion HA antigen

A structurally modified form of the hemagglutinin (HA) antigen that exposes occluded epitopes common to a wide range of influenza viruses. Immunization of immunocompetent humanized mice with this antigen has been shown to induce human cross-reactive antibodies that protect against multiple influenza viruses with different antigenic properties.

Cross-protection

Protection against infection by the host immune system recognizing and eliminating antigens that are new to the host but are closely related to the antigen that previously induced antibody production.

TLR7 adjuvant “DSP-0546LP”

A formulation containing a compound that specifically activates the Toll-like receptor 7 (TLR7), one of the TLR family members, which senses virus-derived RNA and induces innate immune responses. When added to antigens as an adjuvant, it enhances the quantity, quality, and durability of immune responses.

Th1-polarized immune responses

Type 1 helper T lymphocytes (Th1), a subtype of T lymphocytes, predominantly release interferon-γ, and play a critical role in determining the quantity and quality of the antibodies.

Antibody-dependent cellular cytotoxicity (ADCC)

This occurs when the Fc region of antibodies already bound to viral proteins binds to Fc receptors on the surface of effector cells, including NK cells and macrophages. This cellular immune response is one of the critical components of acquired immunity and is considered a crucial mechanism of action by which administered vaccines can eliminate antigens.

About Cyclic Innovation for Clinical Empowerment (CiCLE)

CiCLE aims to formulate innovative infrastructure, including human resources, for accelerating research and development and the clinical application of drug discovery outcomes in ways that precisely match the needs of healthcare professionals as well as to create an environment that empowers the development of open innovation in medical research and development by bringing together Japan's collective strengths through industry-academia-government collaborations.

The joint research project between the NIBIOHN and Sumitomo Pharma (Representative Institution: Sumitomo Pharma), titled "Research and Development of Universal Influenza Vaccine," was adopted in the 4th Public Recruitment for R&D Proposals by the CiCLE in 2019.

6. Paper Information

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(Reference) Fig. 1: Putative mode of action of DSP-0546LP adjuvant

(Source: Excerpt from *Sumitomo Kagaku* 2022, 26 (2022), which is Sumitomo Chemical's technical journal in Japanese)

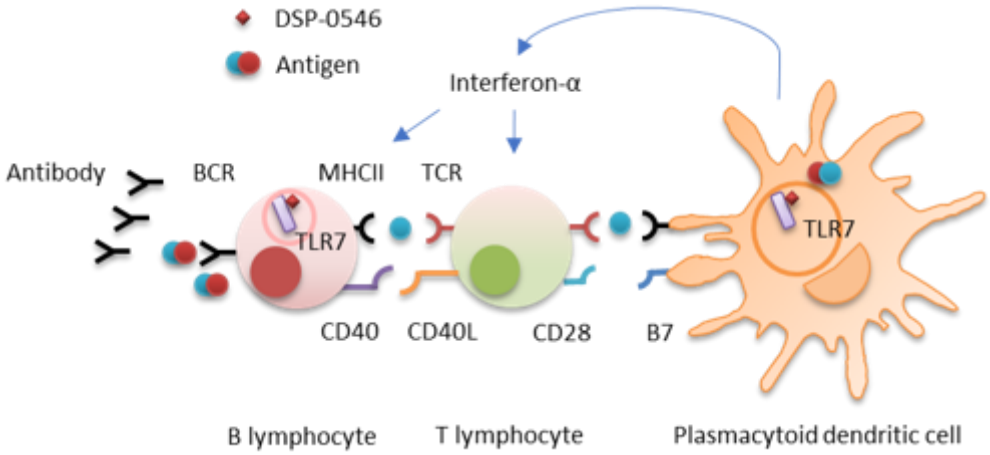
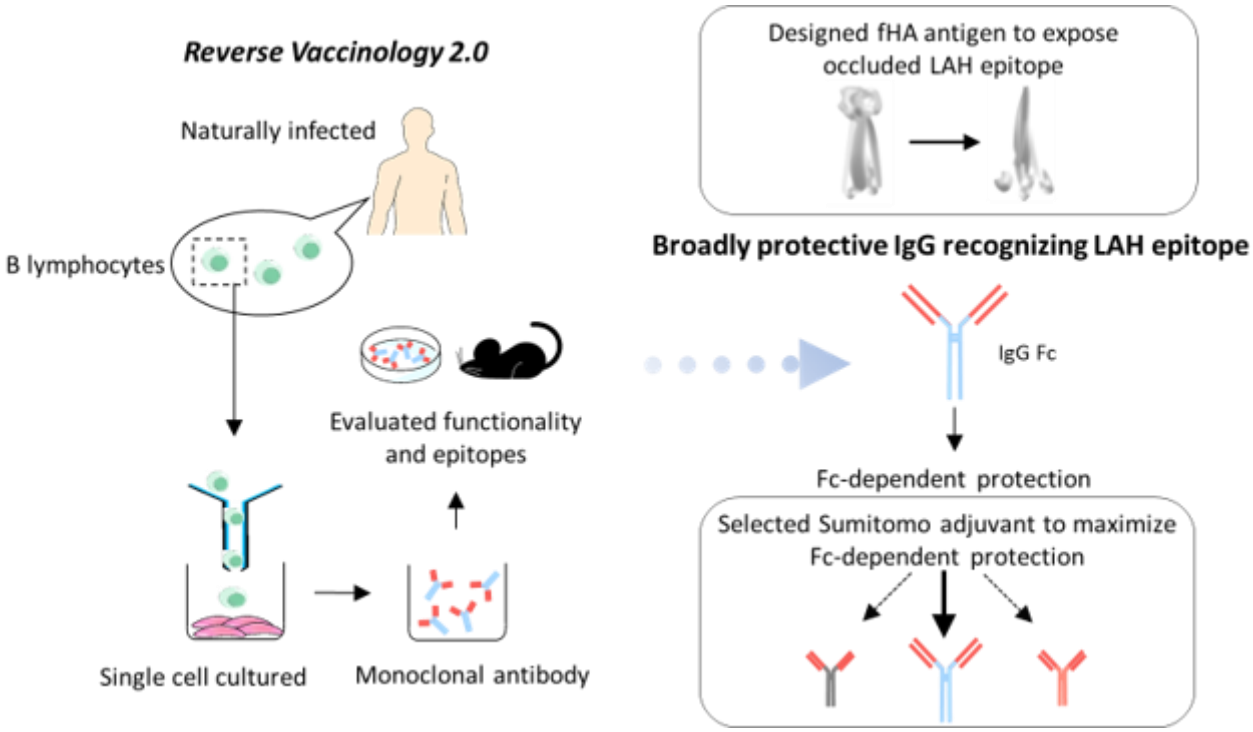


Fig. 2: Putative mode of action of DSP-0546LP-adjuvanted vaccines



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