Novel TLR7 Vaccine Adjuvants: Pandemic Preparedness and Global Health

Sumitomo Pharma. Co., Ltd.
Vaccines
Akihisa FUKUSHIMA

Rational optimization of low molecular weight compounds by chemical analoging and modern formulation technology enables vaccine adjuvants to have limited systemic bioavailability and remain localized for optimal safety and efficacy profiles. We have successfully discovered novel TLR7 vaccine adjuvants, DSP-0546E and DSP-0546LP, based on our expertise in non-clinical and clinical studies of TLR7 agonists. A universal influenza vaccine and several malaria vaccine candidates have been developed in combination with promising antigens designed by adopting the latest approaches, *e.g.*, Reverse Vaccinology 2.0. We are eager to move forward with the research and development of next generation vaccines through collaborative innovation using our new groundbreaking adjuvant technology, in an effort to contribute to pandemic preparedness and global health.

This paper is translated from R&D Report, "SUMITOMO KAGAKU", vol. 2022.

Introduction

Although the global pandemic of COVID-19 was a reminder of the threat of infectious diseases, humans have experienced many large-scale infectious diseases such as the plague, cholera, smallpox, and influenza. Since 1798, when Jenner discovered the first vaccine to prevent infectious disease, the cowpox vaccination method, breakthrough vaccines in various modalities*1 have been developed based on the basic idea of vaccination to prevent infectious diseases. In this article, rational vaccine design based on current vaccinology and novel TLR7*2 vaccine adjuvants (immunostimulants), which are Sumitomo Pharma's technology platform, and universal influenza and malaria vaccines, which are being developed, are introduced.

Evolution of vaccinology and vaccine-based technology

"Life can only be understood backwards, but it must be lived forwards." Soren Kierkegaard

There are also basic concepts in vaccinology, the science of developing vaccines, and there is a need to understand the existence of models in the natural world, pathogens and infectious pathology, as well as the host immune system. For example, lifelong immunity can be established and infection will not occur again for smallpox and yellow fever if recovery is achieved; however, there are also recurring infections such as dysentery and malaria, and these provide clues for designing respective vaccines.

*1 Modality: In the pharmaceutical field, this represents the classification of methods/means of drug discovery technology and includes various molecular-based technologies such as small molecule compounds, peptides, antibodies, nucleic acids, and cells.
*2 TLR7: Toll-like receptors (TLRs) are receptors that sense various pathogens and activates innate immunity, with TLR7 being one of the TLRs that senses RNA derived from viruses and triggers an innate immune response.

Table 1 Adjuvants

Adjuvant	Composition	Target molecule	Vaccines	Reference
Aluminum	Potassium aluminum sulfate, *etc.*	NLRP3	DTaP-IPV, *etc.*	4)
AS01	Monophosphoryl lipid A and QS-21 in a liposomal formulation	TLR4	Shingrix, Mosquirix	5)
AS03	Squalene, α-tocopherol, and PS 80	Unknown	Influenza vaccines	6)
AS04	Monophosphoryl lipid A and aluminum salt	TLR4	Cervarix	7)
MF59	Squalene, PS 80 and Sorbitan trioleate	MyD88	Influenza vaccines	8)
CpG	CpG 1018	TLR9	Heplisav-B	9)
Matrix-M	Saponin in a liposomal formulation	NLRP3	NVX-CoV2373	10)
Algel-IMDG	Imidazoquinoline class molecule and aluminum hydroxide gel	TLR7/8	Covaxin	11)

In general, for infections in which neutralizing antibodies*3 against the target pathogen are induced and passive immunity is established with the transfer of neutralizing antibodies, the expectation is that vaccines will be developed based on antibody induction. For example, for polio vaccine, a live vaccine*4 that induces neutralizing antibodies was developed based on the results of detailed analyses of an experimental model of viral infection in monkeys[1], and the inactivated Japanese encephalitis vaccine that induces neutralizing antibodies was developed based on the results of detailed analyses of a mouse infection model[2]. In cases such as polio and Japanese encephalitis in which a virus enters the body and then reaches the target organ via the blood stream, there may be opportunities for neutralizing antibodies to act on the virus. However, for viruses such as herpes viruses and human T-cell leukemia (HTLV)-1 virus that migrate directly from cells to cells, there is almost no opportunity for antibodies in the blood to act on the pathogen; thus, aiming to prevent these diseases by only transferring or inducing antibodies is considered difficult.

Classically, pathogens that cause infections are isolated and identified from living organisms, and vaccines are prepared through such methods as culturing and inactivation. However, in the 2000s, genome analyses progressed rapidly, and gene sequences of various pathogens were identified. There have also been advances in recombinant technology that have made it possible to produce pathogen components (component vaccines) artificially, efficiently, and at relatively low cost. Furthermore, "Reverse Vaccinology 2.0" *5 that is also a rational antigen design approach that makes full use of human immunology and structural biology has become technically feasible[3].

For a vaccine to be effective, there is a need to appropriately stimulate the host immune system against the pathogen of interest to induce sufficient neutralizing antibody titers and antigen-specific T lymphocytes*6. Even if antigens are rationally designed using the aforementioned "Reverse Vaccinology 2.0," there is often a need to add vaccine adjuvants because appropriate immune induction with antigens alone is difficult. The etymology of the term adjuvant is from the Latin term "*adjuvare*," meaning assist, and adjuvants are widely used as excipients of vaccine antigens because they enhance immune responses or induce qualitatively different immune responses. Aluminum salts, which are still added to many vaccines, were used in humans for the first time as adjuvants in the diphtheria vaccine in 1926. Since then, there has been a lot of research and development on different vaccine adjuvants, which are recognized as one of the important components in vaccines (**Table 1**).

Sumitomo Pharma's adjuvant technology

1. From Sumiferon to the research and development of TLR7 agonists

Sumiferon containing interferon-α[12], which was

*3 Neutralizing antibodies: A general term for antibodies that bind to pathogens and toxins and neutralize biological effects on the host such as infectivity and toxicity. Neutralization usually results in the loss of infectivity and pathogenicity.

*4 Live vaccines and inactivated vaccines: A live vaccine is a vaccine prepared by reducing the toxicity of a living pathogen, and an inactivated vaccine is a vaccine prepared from raw material pathogens that are incapable of infecting (inactivated).

*5 Reverse Vaccinology 2.0: One of the latest theories to enable rational vaccine design by aggregating information on pathogen genomes and 3D structures of antigens, as well as the reactivity of human B lymphocytes and antibodies to antigens.

*6 T Lymphocytes and B Lymphocytes: Lymphocytes are one of the types of white blood cells that specifically recognize antigens. Classified into T lymphocyte and B lymphocytes, T lymphocytes are responsible for cell-mediated immunity and function as a control tower for acquired immunity. B lymphocytes are responsible for humoral immunity and the production of antibodies.

identified as a substance inhibiting viral proliferation in 1957, is a pharmaceutical product for injection to which Sumitomo Chemical (now Sumitomo Pharma) introduced technology from Burroughs, Wellcome & Co (now Burroughs Wellcome Fund) in the United Kingdom in 1980. This was approved for renal cancer in 1987 and the improvement of viremia in patients with chronic active hepatitis C in 1992. In the 1990s, with the progress of immunology, the various biological activities of interferon-α and, in particular, the immunomodulatory activity became clear.

We recognized anew the immunological importance of interferon-α and started a screening study of inducers of interferon-α, considering the potential application in the field of immunology. At the time, we searched for synthetic low-molecular-weight compounds that induced interferon using a method called phenotype screening*7; however, phenotype screening could not be considered very efficient due to the low throughput and high off-target noise. Nevertheless, in 2002, a receptor called TLR7 was reported as recognizing certain low-molecular-weight compounds[13], and the drug discovery research of inducers of interferon-α progressed significantly. With the state-of-the-art technology at the time, artificially producing TLR7 transgenic cells and genetically modified mice became feasible and these were used as drug discovery tools. Several promising new compounds were successfully identified using an approach that enhanced the TLR7-specific agonism of compounds through structural optimization[14), 15]. In addition, toll-like receptors are a group of membrane proteins involved in the recognition of various components derived from pathogens, and TLR7 was found to be involved in the recognition of single-stranded ribonucleic acid (RNA) derived from viruses, *etc.*[16].

In addition to the above findings, we independently demonstrated that TLR7 agonists correct the Th1/Th2*8 balance of the immune system biased toward Th2[17], induced interferon-α in a TLR7-dependent manner, and demonstrated the activation of T lymphocytes, B lymphocytes*6, natural killer (NK) cells*9 and natural killer T (NKT) cells*9 [18]. TLR7 agonists are expected to chemically mimic viral infection and thereby lead to long-term remission in allergic diseases such as bronchial asthma and allergic rhinitis; thus, we conducted clinical studies as a therapeutic agent in allergic diseases with AstraZeneca[19), 20]. In addition, a Phase I study is ongoing in the United States for use as a therapeutic agent in solid tumors.

2. Discovery of novel vaccine adjuvants DSP-0546E and DSP-0546LP

Since pattern-recognition receptors (PRRs) that include toll-like receptors (TLRs), as the name implies, recognize pathogen-associated molecular patterns (PAMPs), ligands with TLR agonist activity are relatively large. For this reason, the effect of chemical modification on the physical properties is often limited. On the other hand, since TLR7 recognizes low-molecular compounds such as imidazoquinoline as described above, there is a large degree of freedom in the design of compounds by chemical synthesis and modification. Through the research and development of therapeutic agents for allergic diseases and solid tumors using TLR7 agonists, Sumitomo Dainippon Pharma (now Sumitomo Pharma; the same shall apply hereinafter) has accumulated a large amount of knowledge related to compound synthesis, nonclinical studies, and clinical studies. In particular, since we have an understanding of the structure-activity relationship, we could reasonably design side chains that would significantly change the properties of the compound while maintaining strong activity. We synthesized a series of compounds in which lipids were chemically cross-linked to TLR7 agonists, and succeeded in identifying a novel pyrimidine derivative TLR7 agonist, DSP-0546, after *in vitro* and *in vivo* screening*10. However, since DSP-0546 is lipophilic due to the chemical cross-linking of lipids, an appropriate formulation is necessary to add sufficient immunopharmacological functions as a vaccine adjuvant. In particular, in order to maintain an appropriate balance between efficacy and safety, there was a need to suppress the excessive inflammatory reactions

*7 Phenotype screening: One of the drug discovery methods to search for compounds, *etc.* based on the phenotype of cells and animals.
*8 Th1/Th2: Type 1 helper T lymphocyte (Th1) and Type 2 helper T lymphocytes (Th2) are T lymphocyte subtypes that are classified according to the type of cytokines (biologically active proteins that are mainly secreted by immune cells) secreted. Th1 is mainly associated with the secretion of interferon-γ, *etc.*, and Th2 with the secretion of interleukin-4, *etc.* These play an important role in determining the quantity and quality of antibodies produced by B lymphocytes.
*9 NK cells and NKT cells: Natural killer (NK) cells are a species of lymphocytes that have the ability to injure tumor cells and virally infected cells. Natural killer T (NKT) cells have characteristics of both T lymphocytes and NK cells.
*10 *In vitro* and *in vivo* screening: Among the drug discovery seeds search (screening) methods, *in vitro* methods use a reaction system in a test tube, *etc.* and *in vivo* methods evaluate reactions in the bodies of living animals, *etc.*

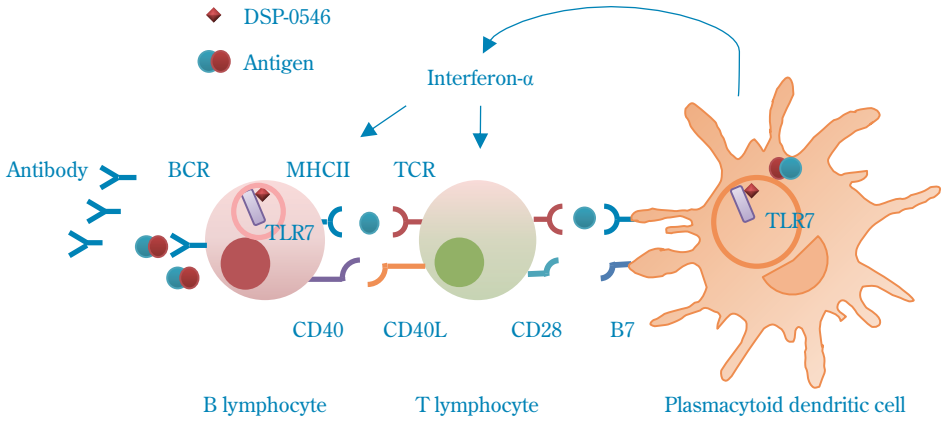

Fig. 1 Putative mode of action of DSP-0546E/LP-adjuvanted vaccines

caused by adjuvant activity as much as possible. Thus, we focused on nanoparticle formulations and carried out various investigations, and finally succeeded in establishing 2 types of formulation in stable oil-in-water emulsion*11, DSP-0546E, and liposome, DSP-0546LP[21), 22)].

Approved adjuvants such as aluminum and oil-in-water emulsions are capable of inducing antibodies; however, there are numerous issues such as being weak at inducing Th1-type immunity, including Type 1 helper T lymphocytes, cytotoxic T lymphocytes, and Th1 type IgG[23)], and difficulty in inducing functional antibodies*12 targeted by some vaccines, including universal influenza vaccines and malaria vaccines. On the other hand, the vaccine adjuvant of Sumitomo Dainippon Pharma is known to induce Th1-type acquired immunity to antigens, that is, antigen-specific pluripotent Type 1 helper T lymphocytes, cytotoxic T lymphocytes, and mouse IgG2 antibodies, *etc*. when added to antigens[24)].

TLR7 is expressed in plasmacytoid dendritic cells, B lymphocytes, *etc*. and stimulating immunocompetent cells via the production of cytokines such as interferon-α as well as direct activation via intracellular signal transduction is thought to facilitate cellular interactions between B and T lymphocytes or plasmacytoid dendritic cells and T lymphocytes, leading to functional antibody production and functional T lymphocytes (**Fig. 1**).

Sumitomo Pharma's candidate vaccines

1. Universal influenza vaccine

Influenza A is a serious respiratory infection resulting in 500,000 deaths every year globally, with economic losses due to pandemic influenza being estimated to be approximately 50 trillion yen[25)]. In the World Health Organization (WHO) Global Influenza Strategy 2019-2030 and the medical area research and development (R&D) promotion plan in Japan, the practical application of a universal influenza vaccine is specified as an example of one of the achievement goals by around 2030[26), 27)]. Current influenza vaccines require annual epidemic viral strain selection, manufacturing, and vaccination based on forecasting of viral antigenic mutations. In addition, there are issues with difficulty responding to novel influenza viruses (**Fig. 2**). Moreover, messenger RNA (mRNA) vaccine technology that was applied to the COVID-19 vaccine is associated with advantages of relatively short manufacturing lead time. However, in the event of a novel influenza pandemic, there is a need to design and manufacture vaccines after genome information becomes available and to spend time for verification through nonclinical and clinical research. Thus, at the earliest, several months is required to implement this in society, and this is not a fundamental solution that can save victims that arise during that time. The social significance of a universal influenza vaccine that is effective regardless of antigenic variation and can solve all of these issues is high; however, this has not yet been actualized.

In recent years, “cross-protective antibodies” that broadly protect against antigen-mutant influenza viruses have been discovered one after another, and several vaccine seeds showing efficacy in animal models have

*11 Oil-in-water emulsion: A solution obtained by dispersing oil droplets in an aqueous phase.
*12 Functional antibodies: An antibody that not only binds to an antigen but also has other functions such as antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

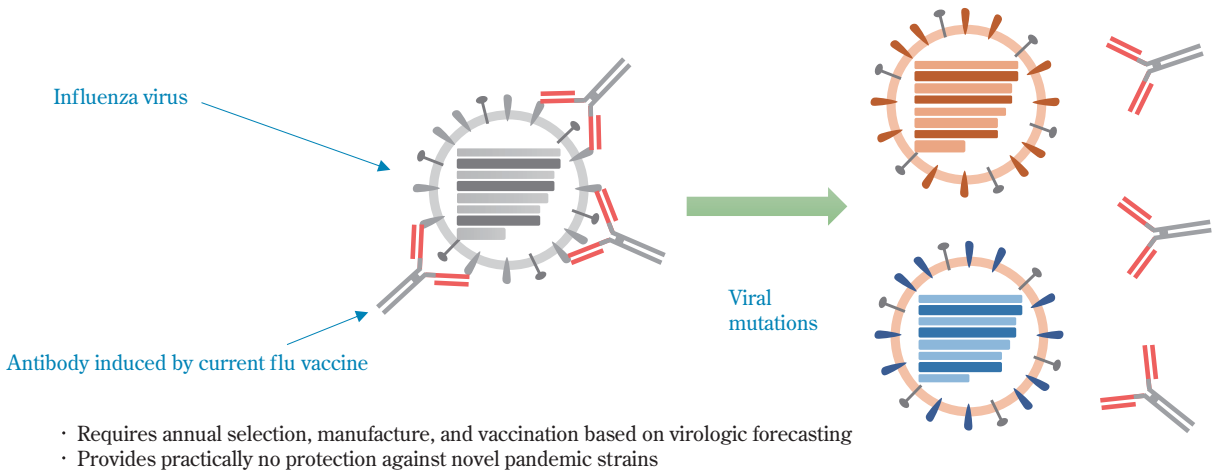

Fig. 2 Issues of current flu vaccines

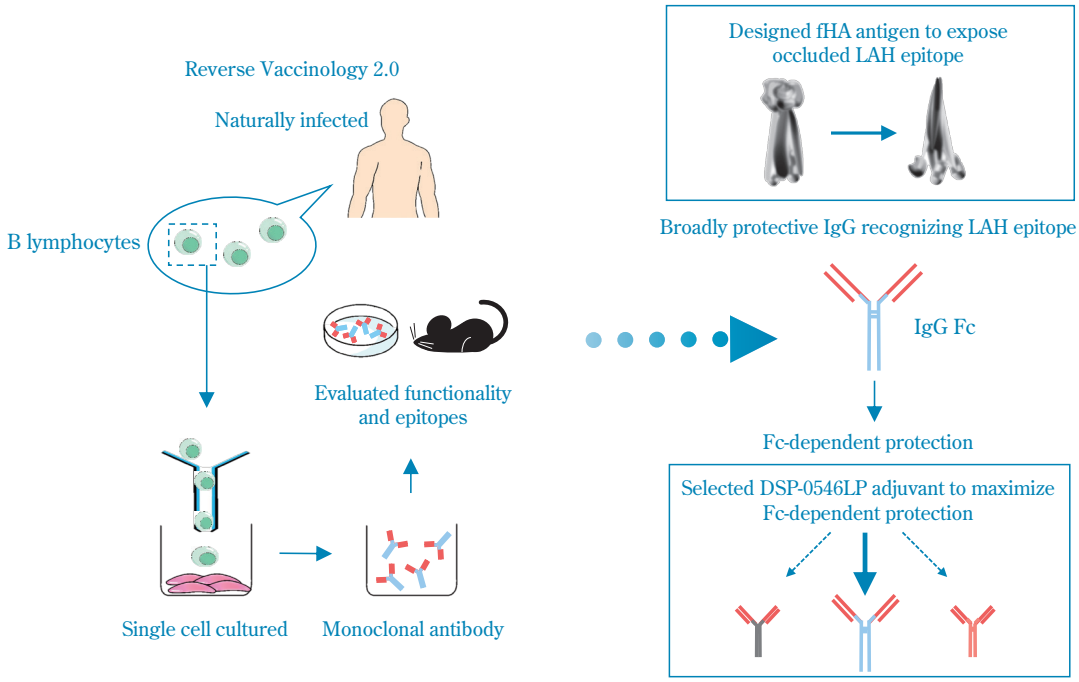

Fig. 3 Identification of a novel universal influenza vaccine candidate

been reported[28)-30)]. However, these vaccine seeds are associated with numerous issues such as the maintenance of complicated higher-order structures and limited epitopes*13 and also issues with practical application, such as efficient methods for inducing functional antibodies. On the other hand, Sumitomo Pharma's universal influenza vaccine candidate adopts a new influenza vaccine antigen, which is different from the complex antigens used to date. The new antigen was discovered by Takahashi *et al.* at the National Institute of Infectious Diseases using an approach incorporating Reverse Vaccinology 2.0 (**Fig. 3**). As a result of detailed analyses of the immune response induced after viral infection, a new epitope (LAH epitope) that induces cross-protective antibodies against various influenza viruses was revealed. Furthermore, a new membrane-fused HA antigen (fHA antigen) that can overcome the issues with conventional universal influenza vaccine seeds was successfully identified[31)]. Sumitomo Pharma and the National Institute of Biomedical Innovation, Health and Nutrition are conducting joint research studies towards the practical application of the universal influenza vaccine

*13 Epitope: A subset of antigens recognized by antibodies, B lymphocytes, and T lymphocytes, also called an antigenic determinant.

with the support of the Cyclic Innovation for Clinical Empowerment (CiCLE) of the Japan Agency for Medical Research and Development (AMED), and are advancing nonclinical research studies including the development of a manufacturing process and an analytical test method for the new membrane-fused HA antigen and a search for biomarkers. By using Sumitomo Pharma's universal influenza vaccine candidate to induce functional cross-protective antibodies and antigen specific Th1-type immune responses, the expectation is to see efficacy against novel influenza strains that have a high likelihood of causing pandemics as well as seasonal influenza. Currently, preparations are underway to start clinical studies as soon as possible.

2. Malaria vaccines

Malaria, one of the world's three major infectious diseases, is a mosquito-borne parasitic disease. In 2019, malaria still affected more than 200 million individuals in the world and caused more than 400,000 deaths[32]. With the spread of antimalarial drugs and epoch-making mosquito nets developed by Sumitomo Chemical Co., Ltd., a decreasing trend in the number of deaths due to malaria was seen starting from around 2005. However, due to the emergence of malaria parasites resistant to existing antimalarial drugs and mosquitoes resistant to insecticides, as well as the confusion caused by the global COVID-19 pandemic, the number of malaria patients in moderately to highly endemic countries of sub-Saharan Africa has been reported to increase from 2019 to 2020[33].

The pathogens of malaria are protozoans of the *Plasmodium* genus, and their life cycle is shown schematically in **Figure 4**. When Anopheles mosquitoes suck blood to lay eggs, sporozoites of malaria parasites accumulated in the salivary glands enter the human body. Sporozoites in the blood invade hepatocytes, proliferate, destroy liver cells and are released into the blood in about ten to thirty minutes. At this time, malaria parasites change into a form called merozoites and invade red blood cells. Merozoites are in ring form, then follow the route of becoming trophozoites and schizonts, and are released by destroying the erythrocyte membrane. Merozoites then enter new red blood cells and divide repeatedly. In addition, some protozoa differentiate into gametocytes, which have sex differences. Sexual reproduction does not occur in the bodies of humans; however, after blood is sucked, these become gametes in the Anopheles mosquitoes' intestines, are fertilized, and undergo changes into zygotes and form oocysts, resulting in the formation of numerous sporozoites. As

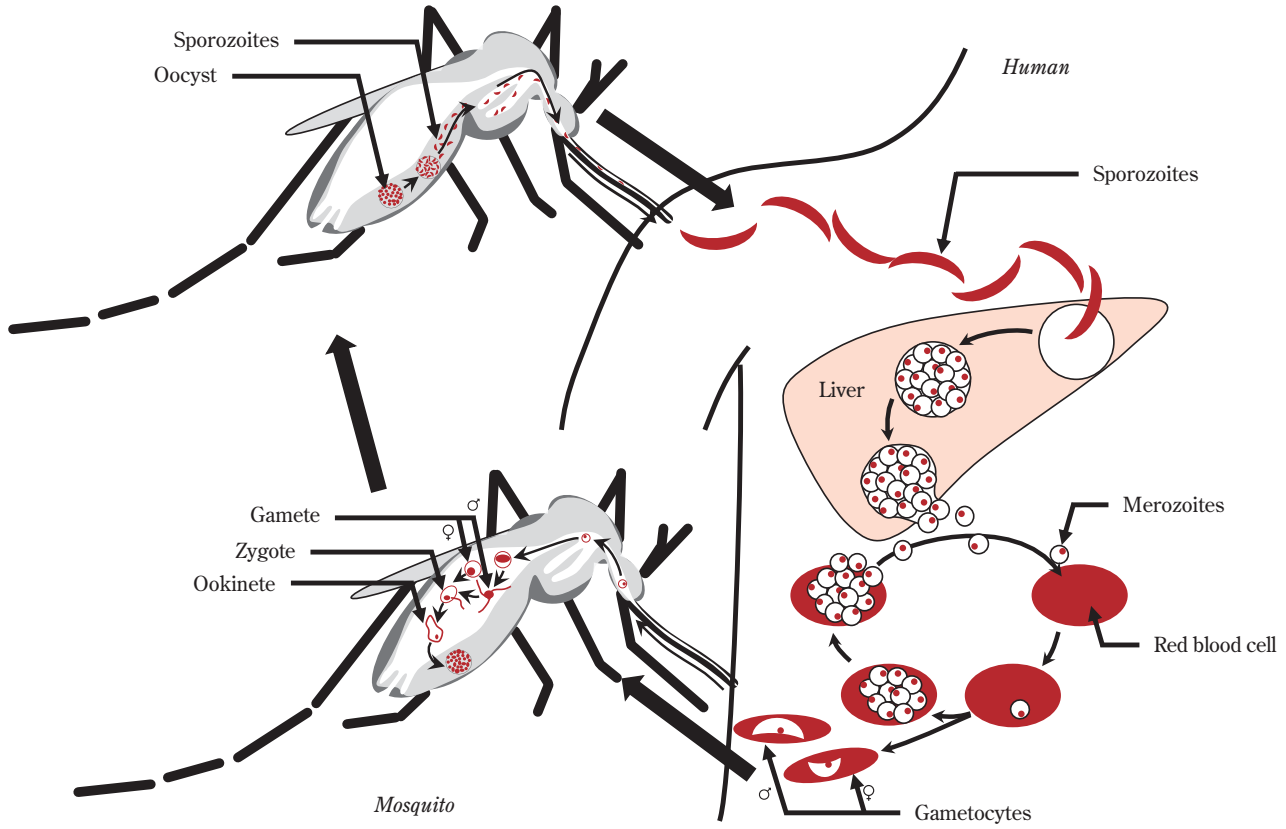

Fig. 4 Malaria parasite life cycle

described above, malaria parasites repeatedly undergo complex morphological changes, and there is a need to design different vaccines for each stage of malaria parasites. There are 3 main types of vaccines: (1) mosquito stage vaccines intended to prevent transmission from humans to mosquitoes, (2) liver stage vaccines intended to prevent infection from mosquitoes to humans, and (3) blood stage vaccines intended to prevent disease onset, with the search for antigens targeted by each vaccine ongoing. The infection protective effect of an inactivated sporozoite vaccine in a mouse malaria model was reported in 1967[34], indicating the possibility of a malaria vaccine. In addition, the malaria parasite genome was revealed in 2002[35] and is expected to accelerate the research and development of vaccines. However, there are numerous issues to overcome due to the complexity of the life cycle of malaria parasites and the protein structure, as well as issues with genetic polymorphism of malaria parasites, and the research and development of malaria vaccines has not progressed as expected. Amid such a situation, the first-generation malaria vaccine, RTS,S/AS01, intended to prevent infection from mosquitoes to humans obtained WHO Prequalification in 2021. However, there is also a report of the effect in preventing severe malaria being approximately 30%[36] and a more effective next-generation malaria vaccine is needed.

Sumitomo Pharma is utilizing novel vaccine adjuvant technology to promote the research and development of 3 different types of malaria vaccines, to prevent transmission, onset of disease, and infection of falciparum malaria, which easily becomes severe and is associated with a high mortality rate. As described above, malaria transmission prevention vaccines, unlike conventional so-called infection prevention vaccines, are intended to prevent transmission from humans to mosquitoes, and are based off of a unique concept of cutting off one of the infection cycles between humans and mosquitoes with malaria parasites. The candidate vaccine formulation for the prevention of malaria transmission from Sumitomo Pharma is a combination of the Pfs230D1+ antigen discovered jointly by Ehime University and the Program for Appropriate Technology in Health (PATH) and Sumitomo Pharma's adjuvant DSP-0546E. Pfs230 is expressed on the cell surface when falciparum malaria parasites turn into gametes in the intestines of Anopheles mosquitoes, and is reported to be a candidate vaccine to prevent malaria transmission[37]. However, Pfs230 has a large molecular weight of 360 kDa and it was difficult to synthesize as a vaccine antigen protein due to the complexity of its structure with a cysteine motif. Tsuboi *et al.* at Ehime University identified the binding region, Pfs230D1+, of a functional antibody with activity to prevent malaria transmission in order to actualize a vaccine[38] and Lee *et al.* at PATH developed a consistent and efficient production method[39]. Sumitomo Pharma, Ehime University, and PATH are conducting joint research and development towards the practical application of this candidate vaccine to prevent malaria transmission with the support of the Global Health Innovative Technology (GHIT) fund, and are producing the Pfs230D1+ antigen and DSP-0546E adjuvant, as well as conducting preclinical studies. Antibodies purified from the serum of animals immunized with our candidate vaccine to prevent malaria transmission have been confirmed to show at least 90% activity to prevent malaria transmission (unpublished data), and is expected to be effective in preventing malaria transmission through functional antibody induction. Currently, preparations are underway to start clinical studies as soon as possible.

The candidate vaccine formulation from Sumitomo Pharma for the prevention of onset of malaria is a combination of the PfRipr5 antigen jointly discovered by Ehime University and Sumitomo Pharma and Sumitomo Pharma's adjuvant DSP-0546E. Although previous vaccine candidates for the prevention of onset of malaria failed to show efficacy due to antigen polymorphism, Tsuboi *et al.* at Ehime University reported that PfRipr is highly conserved in isolates from malaria-endemic areas and that PfRipr is expressed on the surface of merozoite cells[40]. However, since PfRipr contains a lot of cysteine, synthesizing this as a vaccine antigen protein was difficult due to the complexity of its structure. In order to actualize the vaccine, Sumitomo Dainippon Pharma and Ehime University identified the functional antibody binding region PfRipr5 in PfRipr having the activity to inhibit malaria parasite growth and further revealed that PfRipr5 binds to SEMA7A*14 expressed on the surface of human erythrocytes[41]. These achievements enabled rational vaccine design based on the mechanism of action. Process development for antigen production and preparations for the early initiation of preclinical studies are currently ongoing.

*14 SEMA7A: A glycosylphosphatidylinositol-linked semaphorin. This is one of the membrane proteins expressed on the surface of cells.

PfCSP has long been known to be an antimalaria vaccine antigen capable of eradicating the cycle of parasite transmission from mosquitoes to humans, and its partial sequence was used in the first generation RTS,S/AS01 vaccine. On the other hand, flCSP discovered by the Danish Statens Serum Institut in collaboration with PATH is a full-length recombinant protein derived from PfCSP, and its combination with Sumitomo Pharma's adjuvant, DSP-0546E, is expected to lead to higher vaccine efficacy[42]. Sumitomo Pharma, Ehime University, and PATH received support from the GHIT Fund, and are continuing to conduct joint research and development towards the practical use of this malaria infection prevention vaccine, as well as evaluating the efficacy of flCSP/DSP-0546E in a nonclinical model using the RTS,S/AS01 vaccine as a benchmark. The aim is to develop next generation antimalaria vaccines that are more effective than the first-generation vaccine, RTS,S/AS01, and have long-lasting effects.

Contributing to pandemic preparedness and global health

Vaccines are made up of a combination of several fundamental technologies, and which technologies are combined is dependent on the type of pathogen, the pathophysiology of the infection, and the host immune response. mRNA vaccines, which were applied to the COVID-19 vaccines and for which manufacturing approval has been obtained, contain mRNA that encodes antigens as a main component. With a relatively short manufacturing lead time, this is a vaccine-based technology that can be speedy in the event of an emergency; however, in a clinical study in which an mRNA vaccine encoding the G protein of rabies virus was administered using a general injection needle, sufficient neutralizing antibodies were reportedly not induced[43]. In addition, although mRNA vaccines against various infectious diseases including human immunodeficiency virus (HIV) infection are being developed, no vaccines became available for practical clinical use before the COVID-19 pandemic. Furthermore, for antigens for which the conformation of a protein needs to be changed to reveal the binding region of a functional antibody, such as for the universal influenza vaccine under development at Sumitomo Pharma, or antigens for which expression is technically difficult in mammalian cells, the application of mRNA vaccine technology for which protein expression mechanisms are utilized in the human body (intracellular) is thought to be difficult. From a vaccinological point of view, establishing and maintaining various modalities/vaccine-based technologies such as live vaccines, inactivated vaccines, component vaccine technology using genetic recombination technology, vaccine adjuvant technology, and mRNA vaccine technology is considered necessary as crisis management in preparation for a pandemic that may occur in the future.

The universal influenza vaccine under development at Sumitomo Pharma is able to cope with viral antigen mutations, and is thus considered to be one of the effective tools to prevent pandemics caused by novel influenza viruses from normal times before the pandemic. In addition, vaccine adjuvants are one of the components of medical countermeasures (infection crisis pharmaceutical products) that are used not only to enhance the efficacy of vaccines themselves, but also to save the amount of vaccine antigens administered per individual in the event of a pandemic to allow delivery to more individuals (dose sparing) as possible. Sumitomo Pharma's adjuvant technology, when combined with antigens derived not only from the influenza virus and malaria parasite mentioned previously but also from target pathogens, has the potential to be utilized in the development of pandemic vaccines, and is considered to be useful technology to prepare against unknown infections that may appear in the future.

Furthermore, Sumitomo Pharma is advancing research and development for malaria vaccines by utilizing innovative adjuvant technologies to create 3 different types of malaria vaccines and, by combining one or more of these vaccines, the aim is to contribute to the control of malaria, which is one of the most important issues in global health.

Reference

1) D. Bodian, “Viral and Rickettsial Infections of Man”, 3rd. Ed., Lippincott Co., Philadelphia (1959), p.479.
2) A. Oya, Acta Paediatr. Jpn., 30(2), 175 (1988).
3) R. Rappuoli *et al.*, J. Exp. Med., 213(4), 469 (2016).
4) S. C. Eisenbarth *et al.*, Nature, 453 (7198), 1122 (2008).
5) M. Coccia *et al.*, npj Vaccines, 2, Article number: 25 (2017).
6) C. Cohet *et al.*, Vaccine, 7(23), 3006 (2019).
7) N. Garçon and A. D. Pasquale, Hum. Vaccin. Immunother., 13(1), 19 (2017).
8) A. Seubert *et al.*, Proc. Natl. Acad. Sci. USA, 108 (27), 11169 (2011).

9) C. Bode *et al.*, Expert Rev. Vaccines, 10(4), 499 (2011).
10) P. T. Heath *et al.*, N. Engl. J. Med., 385(13), 1172 (2021).
11) B. Ganneru *et al.*, iScience, 24(4), 102298 (2021).
12) A. Issacs and J. Lindenmann, Proc. R. Soc. Lond. B. Biol. sci., 147(927), 258 (1957).
13) H. Hemmi *et al.*, Nature Immunol., 3(2), 196 (2002).
14) Sumitomo Dainippon Pharma Co., Ltd., WO 2005/092893 A1.
15) Sumitomo Dainippon Pharma Co., Ltd., WO 2009/067081 A1.
16) K. A. Fitzgerald and J. C. Kagan, Cell, 180(6), 1044 (2020).
17) H. Matsui *et al.*, J. Immunol., 189(11), 5194 (2012).
18) A. L. Adlard *et al.*, Int. J. Cancer, 135(4), 820 (2014).
19) L. Greiff *et al.*, Respir. Res., 13, 53 (2012).
20) B. R. Leaker *et al.*, Respir. Res., 20, 288 (2019).
21) Sumitomo Dainippon Pharma Co., Ltd., Patent document.
22) Sumitomo Dainippon Pharma Co., Ltd., Patent document.
23) S. G. Reed *et al.*, Nat. Med., 19(12), 1597 (2013).
24) Sumitomo Dainippon Pharma Co., Ltd., WO 2017/061532 A1.
25) V. Y. Fan *et al.*, Bull. World Health Organ., 96(2), 129 (2018).
26) WHO, "Global influenza strategy 2019-2030", https://apps.who.int/iris/handle/10665/311184 (Ref. 2022/3/16).
27) Headquarters for Healthcare Policy, "The Plan for Promotion of Medical Research and Development", https://www.kantei.go.jp/jp/singi/kenkouiryou/senryaku/index.html (Ref. 2022/3/16).
28) F. Krammer, Curr. Opin. Virol., 17, 95 (2016).
29) H. M. Yassine *et al.*, Nat. Med., 21(9), 1065 (2015).
30) A. Impagliazzo *et al.*, Science, 349(6254), 1301 (2015).
31) Y. Adachi *et al.*, Nat. Commun., 10(1), 3883 (2019).
32) WHO, "World malaria report 2020", https://www.who.int/publications/i/item/9789240015791 (Ref. 2022/3/16).
33) WHO, "World malaria report 2021", https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021 (Ref. 2022/3/16).
34) R. S. Nussenzweig *et al.*, Nature, 216(5111), 160 (1967).
35) M. J. Gardner *et al.*, Nature, 419(6906), 498 (2002).
36) WHO, "WHO recommends groundbreaking malaria vaccine for children at risk", https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk (Ref. 2022/3/16).
37) K. C. Williamson *et al.*, Mol. Biochem. Parasitol., 78(1-2), 161 (1996).
38) M. Tachibana *et al.*, Vaccine, 37(13), 1799 (2019).
39) S. Lee *et al.*, Malar. J., 18(1), 356 (2019).
40) E. H. Ntege *et al.*, Vaccine, 34(46), 5612 (2016).
41) H. Nagaoka *et al.*, Sci. Rep., 10(1), 6573 (2020).
42) S. K. Singh *et al.*, J. Biol. Chem., 295(2), 403 (2020).
43) M. Alberer *et al.*, Lancet, 390(10101), 1511 (2017).

PROFILE

Akihisa FUKUSHIMA

Sumitomo Pharma. Co., Ltd.
Vaccines, Senior Officer, Ph.D.