

Vaccine Adjuvant System Technology

Background Information

Adjuvants, from the Latin word *adjuvare* meaning ‘to help’, are compounds used to enhance a vaccine’s ability to elicit a strong, durable, protective immune response making them more effective.

Until recently, vaccine research and development focused nearly exclusively on the antigen, the target molecule that is selected to trigger a specific immune response in the body to protect against a particular disease. It is now widely accepted that adjuvants can also contribute substantially to the immune response induced by a vaccine.

Conventional vaccine adjuvants were mainly based on aluminium salts. However, aluminium adjuvants do not always generate the optimal immune response, and they are often limited in their immunogenic strength.

Recent innovations in molecular science have led to the discovery of a new generation of more powerful adjuvants, opening the door to the development of vaccines for very difficult disease targets. GlaxoSmithKline (GSK) strives to be a pioneer in this exciting new field based on its extensive experience in immunology.

The New Era of Adjuvant Systems

GSK has developed a unique expertise in combining adjuvants to design proprietary Adjuvant Systems, with a view to increasing the immune response to a specific antigen. Within a vaccine, the synergy of the adjuvant system with the antigen aims to optimize the interactions of the vaccine with the immune system to obtain a better, more targeted, immune response.

Adjuvant systems may change the way vaccines will be deployed in the future. The right combination of antigen and adjuvant system can help the body mobilize the optimal immunological pathway to protect against specific diseases in targeted populations.

GSK's Adjuvant System technology is at the heart of a new generation of vaccines which are currently under development. With nearly two decades of experience working with adjuvant systems, GSK scientists can draw on a proprietary portfolio of over 25 adjuvant systems to enrich an expanding vaccine pipeline.

It is hoped that the next wave of novel adjuvant systems will:

- Enhance the immune response (both strong cellular and humoral response)
- Induce long-term persistence of protection (higher and sustained immune response and improved 'immunological memory')
- Provide protection from disease caused by pathogens that have a complex interaction with the immune system (e.g. malaria)
- Improve immune response in people with reduced or suppressed immunity (e.g. enhance immunity in the elderly and in those receiving cancer chemotherapy or who are immunosuppressed)
- Broaden the immune response to allow recognition of virus strain variants
- Reduce the quantity of antigen that is required in the vaccine to elicit an effective immune response or allow for a reduction in the number of vaccine doses needed.

The GSK 'Adjuvant Advantage'

GSK's adjuvant system approach is the most significant leap forward in adjuvant technologies since the 1930s. Over nearly two decades of research into the use of adjuvant systems the company has shown in numerous studies that the benefits of adjuvant systems can be demonstrated both qualitatively and quantitatively.

Adjuvant systems, for example, have been shown to reduce the dosage required to stimulate the body's defenses and create effective immunity to a specific disease. There are clear advantages of dose-sparing and dose-recovery using adjuvant systems, as antigen supplies can be limited. Therefore, effective adjuvant systems are crucial to manufacturing vaccines more quickly and in greater quantities. This improvement of vaccine manufacturing capability may be of particular benefit in a pandemic situation where mass-vaccination is required on very short notice.

Formulated with GSK's Adjuvant System, AS04, *FENDrix*® is the first approved GSK vaccine to contain an adjuvant system. *FENDrix*® was approved by the European regulatory authorities for

the prevention of hepatitis B in a specific high-risk group of pre-haemodialysis and haemodialysis patients, ages 15 years and older. AS04 is also used in GSK's cervical cancer candidate vaccine, *Cervarix*[™].

GSK's Adjuvant System-Enhanced Influenza Candidate Vaccines

For both seasonal and pandemic influenza, GSK is currently investigating candidate vaccines containing novel proprietary adjuvant systems, and for pandemic influenza a prototype vaccine containing a conventional aluminium salt derived adjuvant was developed as well. GSK believes that its novel adjuvant systems will help play a vital role in winning the global battle against the threat of pandemic influenza viruses.

Seasonal Influenza Vaccine

In seasonal influenza, GSK's adjuvant system technology is being investigated for use in an influenza vaccination in the elderly, a group particularly at risk of infection due to a weakened immune response and vulnerability to the potentially severe complications of influenza. The company's novel, proprietary adjuvanted seasonal influenza vaccine candidate shows significant immunological advantages in the elderly when compared to *Fluarix*[®], GSK's standard nonadjuvanted vaccine.¹ This trivalent split vaccine, currently in phase II/III development, uses an adjuvant system to enhance the weak immune responses usually observed in the elderly to reach the levels comparable to those observed in young adults.

An ongoing multinational Phase II / III clinical trial has been designed to investigate whether the immune response induced by this novel adjuvanted influenza vaccine is superior to that induced by *Fluarix*[®] in adults ≥ 50 years. This pivotal immunogenicity trial has enrolled 3500 participants from four countries and the results will form part of the new adjuvanted vaccine licensing file submission.

Pandemic H5N1 Influenza Vaccines

In July 2006, GSK announced interim data from a Belgian clinical trial involving 400 adults showing that its H5N1 pandemic influenza vaccine achieved a high immune response at a low dose of antigen. The candidate pandemic vaccine, which uses a proprietary adjuvant system, enabled over 80% of subjects who received two doses of 3.8 μ g of antigen to demonstrate a strong seroprotective immune response.² This is the first time that such a low dose of H5N1 antigen has been reported to be able to stimulate this level of strong immune response and the

level of seroprotection obtained meets or exceeds target criteria set by regulatory agencies for registration of influenza vaccines.

A large clinical trial with the H5N1 vaccine containing this proprietary adjuvant system was initiated in May 2006 in Europe. This safety study uses a vaccine containing 15µg of inactivated H5N1 and data from this trial is being analysed and will be used to support the planned file submission in Europe.

Pre-Pandemic Influenza Vaccine

In addition to being a strong pandemic vaccine candidate, GSK's H5N1 vaccine containing a proprietary adjuvant system, is also a promising pre-pandemic vaccine candidate, to be used in a proactive pre-pandemic vaccination strategy just before, or immediately after the onset of a pandemic. One of the essential properties of a pre-pandemic vaccine is the ability to cross-protect against variant or 'drifted' strains of the H5N1 virus. Recent clinical trials have shown GSK's pre-pandemic candidate H5N1 vaccine to demonstrate a strong cross-reactive immune response against an evolutionary diverse strain of H5N1 in humans and a cross-protective response in animals.^{3,4}

A license application for this new generation H5N1 pre-pandemic influenza vaccine, containing GSK's novel proprietary adjuvant has been recently filed in Europe, and was accepted for review by the Committee for Medicinal Products for Human Use (CHMP)

Expected benefits of GSK's proprietary adjuvanted candidate vaccine against H5N1

- **Antigen-sparing:** an enhanced performance of the immune system in stimulating a greater response to the viral antigens at lower concentrations of antigen. Such a small quantity of antigen would allow increased production capacity as more vaccines can be manufactured from a fixed amount of bulk antigen, allowing more people to be vaccinated in the event of a pandemic
- **Cross-protection or cross-reactive immunity:** It is hoped that the novel adjuvant system may help to stimulate an immune response that recognises and attacks other viral strains that are similar, but not identical, to the original vaccine virus strain. This is a prerequisite and allows for stock-piling and / or pre-pandemic vaccination

REFERENCES

¹ Leroux-Roels *et al.* Adjuvanted influenza vaccines improve anti-influenza humoral immunity impaired in elderly. International Conference on Influenza Vaccines for the World (IVW) 2006 oral presentation.

² Borkowski A *et al.* Antigen sparing effect of a novel adjuvant system in a split H5N1 pandemic vaccine. *International Vaccines for the World 2006*

³ Leroux-Roels I *et al.* Pandemic influenza preparedness: Cross-reactive immunity with an adjuvanted H5N1 candidate vaccine *International Symposium for Respiratory Viral Infections 2007*

⁴ Baras B *et al.* Cross-protection against heterologous H5N1 challenges in ferrets with low dose adjuvanted split H5N1 vaccine. *International Symposium for Respiratory Viral Infections 2007*

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