

Adjuvants Briefing Paper

Introduction

Vaccines are essential to disease prevention. Diseases such as polio and smallpox killed millions of people around the world until vaccines were developed in the late 19th century. Following the introduction of specific vaccines for these diseases, smallpox has been eradicated and the number of cases of polio has reduced dramatically. More recently, vaccines against previously non-preventable diseases such as rotavirus have started to make significant in-roads into reducing the burden of illness. Despite these successes, there are still many challenges in preventing diseases with vaccines:

- Addressing unmet medical needs in diseases such as human immunodeficiency virus (HIV) that remain out of reach of classical vaccination technologies;
- Developing targeted vaccines for specific populations, such as those with a reduced immune response like the elderly and/or the immunocompromised;
- The need for rapid large scale production in certain situations, for example to protect as many people as possible in an influenza pandemic situation.

Many scientists believe that **adjuvants** may hold the key to solving these problems.

Adjuvants are compounds such as salts of aluminium and are found in many commonly used vaccines. Adjuvants are added to vaccines to enhance the immune response to vaccine antigens. Vaccine antigens teach the body's immune system to recognise and respond with antibodies for the corresponding pathogen that appears foreign and harmful to the body, without us having to become infected with the actual disease. The vaccine adjuvant aluminium (as a phosphate or hydroxide) has been used for over 80 years and help to enhance the body's specific immune response against a pathogen. Learning from nature, scientists have designed novel adjuvants derived from natural ingredients, such as bacteria or plant extracts.

GSK's innovative vaccines using Adjuvant Systems

In challenging situations, a single adjuvant might not be enough to generate the required immune response. Scientists at GSK were amongst the first to combine adjuvants, creating 'Adjuvant Systems' (AS). An Adjuvant System is GSK's combination of two or more types of adjuvants designed to leverage their effect in guiding and enhancing the body's immune response to an antigen, thereby delivering enhanced and sustained protection in a vaccine.

The Benefits of Adjuvants

GSK's Adjuvant Systems have been shown to offer an improved quality of the immune response by inducing a more enhanced, targeted stimulation of the immune response to produce strong, sustained and broad protection, which can:

- Provide **protection against challenging diseases** formerly thought to be beyond the reach of vaccination (e.g. GSK's malaria candidate vaccine RTS,S where for the first time there is evidence that a vaccine against a parasite is feasible);
- Offer patients potential **broader protection** or cross-protection against related disease-causing pathogens, so-called 'smarter' immunity (e.g. Cervarix™ where the vaccine tackles multiple HPV types that cause cervical cancer);
- **Enhance vaccine protection** by providing a high and long term persistence of protection (e.g. Cervarix™);
- To **improve immune response** in poorly responsive populations such as the immunocompromised or the elderly (e.g. FENDrix® where vulnerable patients with chronic kidney disease show a less frequent need for hepatitis B booster doses);and
- In some cases, **reduce the amount of antigen needed** in a vaccine, enabling an increase in the manufacturing capacity, which may be necessary in a public health emergency in order to be able to vaccinate more people more rapidly (e.g. in an influenza pandemic with pre-pandemic and pandemic vaccines).

GSK's proprietary Adjuvant Systems have been used to develop some of the world's most advanced vaccines and candidate vaccines. GSK has four Adjuvant System families that are either registered or in late phase development: AS01 used for instance in GSK's candidate malaria vaccine, AS03 used in GSK's pandemic flu vaccines, AS04 used in GSK's cervical cancer vaccine Cervarix™ and AS15 used in GSK's candidate cancer therapeutic vaccines. These four families have been specifically designed to promote the type of immune response required according to several criteria: disease, target population, host/pathogen interaction, route of administration and the required characteristic of the immune response. This portfolio forms the heart of a new generation of vaccines both preventative and therapeutic vaccines specifically designed to prevent or treat diseases in new ways and prevent sickness in people young and old, around the world.

Are Adjuvants Safe?

A number of concerns have been expressed regarding the safety of adjuvants. GSK is confident in the safety profile of its vaccines containing Adjuvant Systems and has shared and continues to share the extensive safety data it has accumulated with health authorities worldwide. GSK also posts the study results of registered vaccines formulated with Adjuvant Systems on its Clinical Trial Registry available on the gsk.com website. From a general perspective, the adverse events reported after administration of Adjuvant System adjuvanted vaccines are very much in line with what has been observed with other vaccines such as aluminium adjuvanted vaccines. Among the most frequently reported general symptoms are headache, fatigue and myalgia (pain). General symptoms and most local symptoms such as pain and redness at the site of injection typically are mild or moderate in intensity and of short duration. Overall, GSK's Adjuvant System adjuvanted vaccines are well tolerated and their safety profiles clinically acceptable.

GSK has a strong track record in the research and development of vaccines. GSK's vaccines are supported by extensive clinical and post-marketing data relating to the millions of people vaccinated worldwide, and they continue to be evaluated in well-designed clinical studies:

- Over 10 million doses of Cervarix™, which contains Adjuvant System AS04, have been distributed worldwide with over 1.4m doses administered under the UK national immunisation programme; and
- As of March 2010, it was estimated that 29 million people have received the GSK pandemic H1N1 vaccine Pandemrix™, which contains AS03, as part of government-initiated vaccination programmes across Europe.¹ Governments outside Europe are using GSK's vaccine Arepanrix™ H1N1, which also contains AS03.

The Future of Vaccines using GSK's Adjuvant Systems

GSK is applying the technology and experience gained from developing adjuvants for vaccines to develop new therapies for diseases such as cancer, where treatment options are limited. Cancer is the leading cause of death worldwide, with more than one in three people developing some form of the disease during their lifetime. GSK is developing a potential new class of cancer therapy designed to educate the patient's own immune system to fight cancer. This is known as a cancer therapeutic vaccine or cancer immunotherapy. This treatment works by inducing, enhancing, or suppressing an immune response. GSK is currently developing a cancer immunotherapy approach called Antigen Specific Cancer Immunotherapeutics (ASCIs). ASCIs contain cancer-specific antigens and the AS15 Adjuvant System that has been specifically selected to enhance the strength and duration of the immune response. The most advanced ASCI in development aims to induce an immune response towards MAGE-A3 tumour-specific antigen, and is now in phase III trials in both non-small cell lung cancer and melanoma.

April 2010

¹ European Medicines Agency. Fourteenth Pandemic Pharmacovigilance Update EMA/190452/2010. 24 March 2010