Crucell

Developing a malaria vaccine

March 2011

There is currently no licensed vaccine to protect people against malaria, a disease caused by infection with the Plasmodium parasite and transmitted by mosquitoes. Therapies are available for malaria patients, but the worsening problem of drug resistance in many parts of the world is making adequate treatment and control of malaria increasingly difficult. In addition, many insecticides are no longer useful against the mosquitoes that transmit the disease.

Crucell is working in collaboration with a number of research groups to develop a safe, effective and affordable vaccine against Plasmodium falciparum, the most lethal of the four species of malaria parasite that infect humans. Crucell's approach is based on our innovative AdVac® technology, which uses harmless adenoviruses as vaccine delivery vehicles (vectors).

Towards an AdVac®-based malaria vaccine

Crucell's first collaboration aimed at malaria vaccine research was born in March 2003, with the Walter Reed Army Institute of Research (WRAIR) and GlaxoSmithKline Biologicals (GSK). In a collaborative preclinical study, we tested a candidate AdVac®-based malaria vaccine as a stand-alone vaccine and in combination with GSK's RTS,S malaria vaccine candidate. These studies showed that Crucell's AdVac® vaccine efficiently primed and/or boosted malaria-specific immune responses.

In March 2004, the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health NIH, agreed to support the development of Crucell's AdVac®-based malaria vaccine.

In partnership with the NIAID, Crucell's candidate malaria vaccine entered a Phase I trial in the USA in the final quarter of 2006. Volunteers were recruited by two centers: Vanderbilt University in Nashville, Tennessee, and Stanford University in Palo Alto, California. Boost vaccinations for the final group of volunteers were completed in December 2009. Analysis of unblinded safety data revealed a good safety profile. Available immunogenicity data indicated that the AdVac®-based vaccine triggers both humoral and cellular immune responses. Extensive (pre-)clinical studies have demonstrated the complementary role and necessity of anti-CS antibody and T-cell mediated immune responses in the ability to protect against malaria. The tested vaccine consists of an adenovirus 35 (Ad35) vector delivering protein from the circumsporozoite (CS) stage of the P. falciparum parasite to the immune system.

In July 2009, Crucell announced a new collaboration with the US-based Malaria Vaccine Initiative and the United States Agency for International Development (USAID) Malaria Vaccine Development Program (MVDP) to accelerate development of a promising new type of malaria vaccine. With USAID MVDP funding, the partners are conducting studies to determine the effectiveness of Crucell's novel prime–boost vaccine approach targeting P. falciparum. The studies explore the efficacy of two different adenovirus vectors, Ad35 and Ad26, as mechanisms for delivering CS protein.

In May 2010, the Ad35-CS malaria vaccine candidate Crucell is developing in collaboration with the NIAID, entered a Phase I clinical study in Burkina Faso, Africa. This is the first study evaluating the safety and immunogenicity of this AdVac®-based vaccine in an area where malaria is endemic and the healthy adult population can be assumed to be semi-immune to malaria.

Exploring a combination vaccine strategy

In April 2010, Crucell and GlaxoSmithKline Biologicals (GSK) signed a binding letter of agreement to collaborate on developing a second-generation malaria vaccine candidate. Preclinical data have indicated that immune responses against the malaria parasite—specifically, the circumsporozoite stage of P. falciparum—are significantly enhanced when Crucell's AdVac® technology and GSK's RTS,S/AS technology are used in combination, versus either component.

Under the terms of the agreement, Crucell will contribute its recombinant malaria vaccine candidate, Ad35-CS, which is based on Crucell's AdVac® technology and PER.C6® manufacturing platform. GSK will contribute its late-stage malaria vaccine candidate RTS,S/AS, which is based on P. falciparum circumsporozoite surface antigen.

Production of an AdVac® malaria vaccine

Crucell's AdVac®-based malaria vaccine is made by inserting selected parts of the malaria parasite into an adenovirus vector, which acts as a 'vehicle' for vaccine delivery. AdVac® technology uses adenoviruses that very rarely infect humans, thereby avoiding the potential problem of pre-existing immunity to the viral vector.

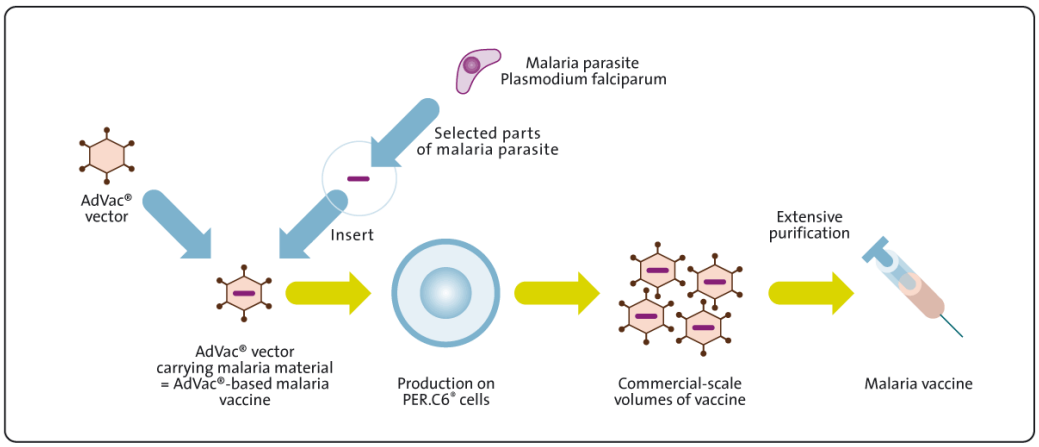

Figure 1. Malaria vaccine production process

The AdVac® vector carrying genetic material from the malaria parasite cannot replicate independently, but it replicates abundantly and rapidly when inoculated into PER.C6® cells. (Crucell's PER.C6® human cell line technology has been developed to facilitate and improve the commercial-scale manufacture of biopharmaceuticals.) The resulting product undergoes extensive purification before use as a vaccine.

This method of vaccine production has significant safety advantages over alternative methods, and results in a vaccine that can trigger a strong immune response against the disease-causing microorganism. The steps used in producing an AdVac®-based malaria vaccine are outlined in a simplified form in the following diagram.