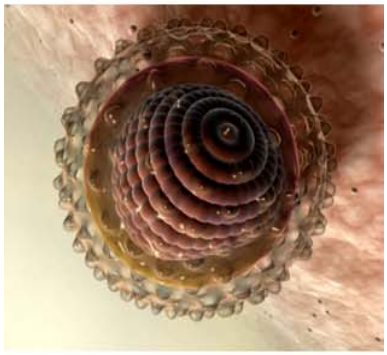
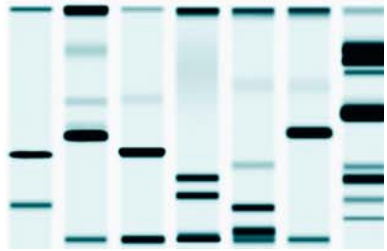
GSK's malaria vaccine – a positive step for novel adjuvant systems?





LONDON, UK----18 December 2008----ExpertREACT. The advancement of GSK Biologicals malaria vaccine candidate (RTS, S/AS) to planned Phase III studies is groundbreaking news given the huge burden of disease. Because the vaccine contains MPL and QS21, the progress might also strengthen the company's argument for a widespread commitment to novel adjuvant systems

A few weeks back, new clinical results related to GSK Biologicals RTS, S/AS malaria vaccine candidate were released with high profile in the New England Journal of Medicine (NEJM) **(1).** RTS, S/AS, which is being developed in collaboration with the PATH Malaria Vaccine Initiative (MVI), is the most advanced malaria clinical candidate available. With the results of two new Phase II trials in both infants (< 1yrs) and children aged 5 to 17, RTS S/AS appears to lower the risk (>50%) of malaria clinical episodes after long follow-up and most importantly, appears to have an encouraging safety profile. The vaccine (3 doses) also does not appear to interfere with the protective immune response to the vaccine components for Diphtheria (D), Tetanus (T), whole cell pertussis (Pw) and *haemophilus influenzae* (Hib) which are commonly administered as part of the WHO Expanded Program on Immunization (EPI) in countries where malaria is endemic. GSK Biologicals now plan to use one formulation of the vaccine (RTS, S/AS01) for larger Phase III trials on track to start in 2009.

Beyond the important advancement of actually demonstrating efficacy of their malaria vaccine, **VacZine Analytics** believes the results might also influence GSK's global push to gain acceptance of their novel adjuvant systems that contain either MPL (3-O-desacyl-4'-monophosphoryl lipid A) and QS-21 (Stimulon system) or a combination of both. Of the major vaccine players GSK Biologicals appear to be the most committed to novel adjuvants with an estimated greater than 60% of their R&D pipeline containing one of their proprietary MPL-based systems. The company which invested an initial $300m acquisition cost in Corixa in 2005 (2) is keen to realize the potential of MPL, especially within their HPV vaccine, Cervarix which has met some resistance gaining approval in the critical US market.

For GSK, the use of MPL/QS-21 in the malaria program is validating fundamental scientific arguments supporting novel adjuvants. These arguments are becoming strengthened with convincing clinical data in randomized clinical trials. In contrast to the restricted range immune responses or Th2 type induced by the standard adjuvant "alum", MPL is reported to induce cell mediated responses (CMI) or Th1 type bias which is critical for protection and pathogen clearance in complex diseases. In the case of GSK's malaria vaccine, this cell response is believed to interfere with the intra-hepatic stage of the malaria parasite. While GSK openly promote the added value of MPL in their Cervarix HPV vaccine, the adjuvant along with QS-21 appears more convincing and necessary in RTS, S/AS01. This is because the vaccine mechanism of action is more dependent on the inclusion of novel adjuvant than in the case of HPV which can be effective with alum alone re: Merck & Co's Gardasil.

In the West the acceptance of novel adjuvant systems and the views of US and European (EMEA) vaccine regulators is a widely discussed, controversial topic. It appears there are differing concerns with the potential unexpected adverse events related to novel adjuvants, especially if given to otherwise healthy populations. The US FDA takes a cautious view and is yet to approve a new vaccine adjuvant because largely their mechanisms of action are not fully known. Along with their hesitation on Cervarix, the agency recently put on hold Merck & Co's Phase III investigational hepatitis B vaccine (Heplisav, V270) due to one case of excessive inflammation (Wegener's granulomatosis) possibly linked to the immunostimulatory DNA component (3). The EMEA has approved vaccines with novel adjuvants including GSK's Cervarix and previously Chiron's (Novartis) MF-59 adjuvanted flu vaccine, Fluad, although Novartis Vaccine halted a Phase III study (EU) of Fluad in a pediatric population (4).

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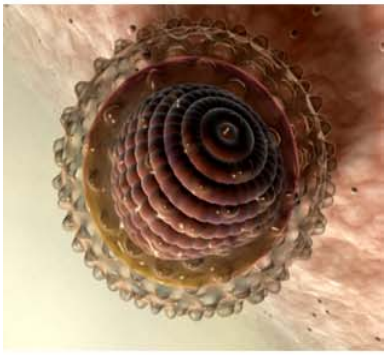
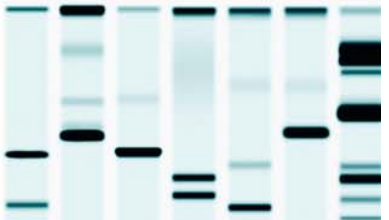
QS-21, extracted from a South American tree, *Quillaria saponaria* is not contained within an approved vaccine but has been shown to be a powerful T-cell stimulant. There have been some reported issues related to QS21 safety and injection site reactogenicity. In one notable study investigating a human Alzheimer's disease vaccine trial deaths occurred due to encephalitis occurred although the exact contribution of QS21 has not been established **(5).**

The fact that GSK's malaria vaccine, which contains both MPL and QS-21, is being tested in African infants therefore raises important considerations to Western regulators, especially since it was first tested by US volunteers as part of collaboration with the US Walter Reed Army Institute of Research (WRAIR). It exemplifies how the perception of vaccination risk versus vaccination benefit varies dramatically around the globe with the psychological "bar" of safety unfortunately being much lower in the developing world. If proven to be effective and safe in Phase III and eventually licensed for use, RTS, S/AS theoretically would be given to millions of young children. Even in the West, a vaccine given on such a large scale has been associated with unexpected rare adverse events e.g. Rotashield. Another key question is whether the vaccine will be then licensed for Western travellers and/or military use. Individuals that are used to a high level of adverse events commonly related to antimalarial drugs – will they accept the same risk from a newly developed vaccine?





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4) Vaccine Pipeline Review (CAT No: VAVS011), October 2008. Published by VacZine Analytics

5) Ghochikyan A, Mkrtichyan M, Petrushina I, Movsesyan N, Karapetyan A, Cribbs DH, Agadjanyan MG. Prototype Alzheimer's disease epitope vaccine induced strong Th2-type anti-A beta antibody response with Alum to Quil A adjuvant switch. Vaccine 2006;24: 2275–2282.

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VacZine Analytics is a new strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.