

Editorial

Malaria and the Challenges of Vaccine Development

Malaria kills more than one million people every year, especially children and pregnant women. The life cycle of malaria begins during the bite of an infected mosquito when sporozoites are injected into the blood stream. They are cleared from the circulation within a very short period with many of them entering the liver where they develop into the liver stage merozoites. Thousands of these merozoites rupture infected hepatocytes and invade the red blood cells to begin the blood stage of the disease. The various toxins and cytokines produced during the blood stage of the disease are responsible for its symptoms and pathology. Some of the blood stage merozoites may develop to form gametocytes or the sexual stages. When these gametocytes are ingested by the mosquito during a blood meal, they develop within the mosquito to the sporozoite stage, which then migrate to the salivary gland from where they are transmitted to another host. Attempts at eradicating the disease with insecticides and chemotherapeutic drugs failed because of the emergence of drug-resistant parasites and *Anopheles* mosquitoes that are resistant to insecticides.

Consequently efforts were made to develop vaccines against the parasite as a cheap means of combating the disease. Three main strategies were adopted for developing malaria vaccines. The first involves vaccines that would neutralize sporozoites as they enter the blood stream thereby rendering them incapable of invading the liver. This vaccine has the potential of preventing infection completely. The second strategy involves producing vaccines against the blood stages of the parasite. These vaccines can only

limit the invasion of erythrocytes and produce mild disease but would not prevent infection. The third strategy uses transmission blocking vaccines. These vaccines stimulate the production of antibodies against the sexual stages thereby rendering them sterile within the mosquito and incapable of infecting a host during a blood meal. Actually, the vaccines that have received the most attention are those directed against the sporozoite stage of the parasite. Indeed, γ -irradiated sporozoites are highly immunogenic and have been shown to protect against challenge with viable sporozoites. However, it is cumbersome to produce the amount of purified sporozoites that would be required for large scale immunization. In order to overcome this limitation, the immunodominant repetitive epitope of the sporozoite, the circumsporozoite (CS) protein was adopted as a vaccine candidate. Unfortunately, not everyone is capable of raising high antibody levels against the CS protein because it is genetically restricted. Consequently, not everyone is protected when immunized with the CS protein. Another problem with the CS protein as a vaccine candidate is that it fails to prime appropriate The cells that would ensure natural boosting of antibody production when infected with sporozoites. This means that as soon as majority of the antibody is degraded, immunity is also lost.

An attempt to overcome these problems resulted in the formulation of the current vaccine candidate, RTS,S/ASO2A which is also based on the CS protein. It is the vaccine candidate for which clinical development is most advanced. RTS,S consists of a hybrid molecule

recombinantly expressed in yeast, in which the CS protein and its carboxyl-terminal regions are fused to the N-terminal of the S antigen of hepatitis B virus (Hbs Ag) in a particle that also includes the un-fused S antigen. ASO2A is an adjuvant consisting of an oil-in-water emulsion containing the immunostimulants monophosphoryl lipid A and *Quillaja saponaria* fraction 21 (QS21). As expected of such a super antigen, high levels of anti CS protein antibodies were produced in clinical trials. However, as in previous CS protein vaccination trials, not all individuals produced high levels of antibody. Consequently, only those with high levels of antibody were protected against malaria while those with moderate levels of antibody experienced delayed onset of the disease. Therefore, it is doubtful if RTS,S/ASO2A will meet the requirements of a malaria vaccine for widespread use.

It may be necessary to revisit the irradiated sporozoite as the answer to the malaria vaccine

question. All vaccination experiments conducted so far have shown that the sporozoite evokes very strong protective immune response and it is not genetically restricted. The major problems are likely to be the generation of large quantities of sporozoites, purification to ensure that they are free of mosquito debris, the requirement for the sporozoites to remain viable during storage until used, and the fact that they are only immunogenic when inoculated through the intravenous route. A sporozoite vaccine would be highly beneficial to infants and young children since they are more likely to develop immunity to the parasite similar to those of immune adults faster as a result of early exposure to the parasite.

Professor Patrick O. Uadia
Department of Biochemistry
University of Benin
Benin City 300001
Nigeria.
Email: psouadia@uniben.edu