

Background and Summary Paper

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Live Attenuated Malaria Vaccine Designed to Protect through Hepatic CD8+ T Cell Immunity

JE Epstein, K Tewari, KE Lyke et al.

Plasmodium falciparum malaria causes illness in more than 250 million people and kills over 800,000 each year, mostly African children. In addition, malaria is a serious health concern for travelers and military personnel deployed to malaria endemic areas.

An effective vaccine to prevent malaria infection is considered the only tool that will eventually conquer this terrible disease. A major step will be to develop a malaria vaccine, which is highly effective at preventing infection. Such a vaccine would provide immediate benefit to recipients of the vaccine, and be used for elimination of *Plasmodium falciparum* malaria in geographically defined areas by preventing transmission. To be effective in eliminating the infection, any vaccine must prevent infection in greater than 80% of recipients for at least 6-24 months.

To date, such high level of protection has only been achieved in humans who were immunized by the bite of mosquitoes that inoculated live, sporozoite stage *Plasmodium falciparum* parasites that had been weakened by irradiation or treated immediately with drugs after multiple exposures. Immune cells called cytotoxic or killer CD8+ T cells that are activated in humans by the sporozoites are responsible for the protection against malaria after immunization with irradiated sporozoites.

We know however, that it is not feasible to immunize large numbers of humans by bite of mosquitoes carrying sporozoites, and it had been thought to be impossible to manufacture a whole sporozoite vaccine that met regulatory standards of purity, sterility, potency and safety. Therefore, until the study reported in this paper (*Science*, www.sciencexpress.org, Sept. 2011), no humans had been immunized with a sporozoite vaccine administered by inoculation with a needle and syringe, even though immunization with sporozoites produces such potent protective immunity.

Sanaria developed a manufacturing process that meets current Good Manufacturing Practices mandated by the FDA. This process was used to produce the vaccine for the trial reported herein. The vaccine is composed of attenuated (weakened) malaria sporozoites that are the stage transmitted to humans by mosquitoes.

The work described in the paper by Epstein, Tewari, Lyke and colleagues demonstrates that:

1. The Sanaria[®] PfSPZ Vaccine composed of intact, radiation attenuated (weakened) *Plasmodium falciparum* (Pf) sporozoites (the malaria parasite developmental stage transmitted to humans by mosquitoes) can be manufactured in accordance with FDA standards for clinical testing. This is the first time such a vaccine has been manufactured.
2. Sanaria[®] PfSPZ Vaccine was safe and well tolerated in this Phase 1 clinical trial in humans. This is the first time humans have received such a vaccine.

3. Sanaria[®] PfSPZ Vaccine administered in the skin by needle and syringe to humans was immunogenic and protective, but not nearly to the levels found after mosquito bite immunization.
4. When the Sanaria[®] PfSPZ Vaccine is administered by intravenous injection by needle and syringe to animals, the sporozoites trigger extremely high levels of malaria parasite-specific cytotoxic (killer) CD8+ T cells in the liver that can confer high levels of protection.
5. The Sanaria[®] PfSPZ Vaccine is highly potent.

This work provides the foundation for the next clinical trials in which the PfSPZ Vaccine will be administered intravenously to volunteers in the USA and Africa, and the initiation of planning to use the PfSPZ Vaccine for geographically focused *Plasmodium falciparum* elimination campaigns.