Experimental vaccine blocks transmission of malaria in mice: study

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Researchers at the National Institutes of Health have developed an experimental vaccine that could, theoretically, eliminate malaria from entire geographic regions, by eradicating the malaria parasite from an area's mosquitoes.

The vaccine, so far tested only in mice, would prompt the immune system of a person who receives it to eliminate the parasite from the digestive tract of a malaria-carrying mosquito, after the mosquito has fed upon the blood of the vaccinated individual. The vaccine would not prevent or limit malarial disease in the person who received it.

An article describing this work was published on the Web site of *Proceedings of the National Academy of Sciences*. The vaccine was developed with conjugate technology, which joins or "conjugates" molecules the immune system has great difficulty recognizing to molecules the immune system can recognize easily. Primed by the conjugate vaccine, the immune system begins making antibodies—immune proteins that target specific molecules. The antibodies then eliminate molecules the immune system would fail to detect.

"With conjugate technology, NIH researchers have developed effective vaccines against such scourges as Haemophilus influenzae type B meningitis and typhoid fever," said Elias A. Zerhouni, M.D., Director of the National Institutes of Health. "The experimental malaria vaccine shows great promise for combating a terrible disease that exacts a

devastating toll on the world's children."

The vaccine was developed by researchers in the National Institute of Child Health and Human Development's Laboratory of Developmental and Molecular Immunity, in partnership with researchers in the Malaria Vaccine Development Branch of the National Institute of Allergy and Infectious Diseases (NIAID), and the Biotechnology Unit of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The study authors wrote that malaria kills more than one million children each year. The disease can result in severe headache, high fever, chills, and vomiting. Malaria is caused by a single celled parasite, Plasmodium. In all, four species of Plasmodium cause malaria in people, with Plasmodium falciparum causing the most severe form. The malarial parasite spends part of its life cycle in humans, and part in mosquitoes. The parasite is injected into an individual by the bite of an infected mosquito. Numerous experimental vaccines have been tried against the form of the parasite that resides in humans, but have been unsuccessful or produced limited immunity. The Plasmodium cells escape the human immune system by hiding in liver and blood cells, making them difficult to target with a vaccine. During the human phase of the infection, these cells, for the most part, exist in an asexual form.

Some of the Plasmodium cells, however, transform into gametocytes—the sexual forms of the parasite that are equivalent to sperm and eggs. Fertilization takes place in the mosquito gut, after which the parasite imbeds itself in the gut lining. There, it passes through discrete stages, before migrating to the insect's salivary glands, where it is passed on to the next host through a mosquito bite.

The protein Pfs25 (Plasmodium falciparum surface protein 25) is found only on the surface of the ookinette, a stage of the parasite living in the mosquito gut, and does not appear on any other stage of the parasite.

When injected into human volunteers, Pfs25 fails to generate a sufficient level of antibodies to target the parasite.

In their article, the researchers described several strategies for using conjugate technology to make an effective vaccine based on Pfs25. These consisted of chemically linking numerous Pfs25 molecules to each other and to other proteins: Pseudomonas aeruginosa exotoxin A, a protein from a species of bacteria that infects people with weakened immune systems, and ovalbumin, a protein found in egg whites. All of the conjugates produced high levels of antibodies in mice. Adsorbing the conjugate molecules to the surface of molecules of aluminum hydroxide produced even higher levels of antibodies. (Adsorption is a chemical process in which one molecule accumulates on the surface of another, forming a molecular or atomic film.)

The researchers also discovered that the ability of the mice to produce antibodies to the vaccine increased with time. In fact, the animals produced higher levels of antibodies when they were tested three and seven months after their initial set of immunizations than they did one week after their immunizations were completed.

Next, the researchers fed serum containing the antibodies to mosquitoes carrying Plasmodium falciparum. (Serum is the fluid from which blood cells and clotting factors have been removed.) Microscopic examination of the mosquito digestive tracts revealed that the antibodies were capable of completely eliminating the ookinettes.

The study authors noted that Psv25H, a molecule similar to Pfs25, is found on the surface of ookinettes of another species of Plasmodium that causes malaria, Plasmodium vivax. They wrote that the conjugate technology could be easily adapted to make a vaccine against Psv25H.

Source: National Institute of Child Health and Human Development