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New Approach to Malaria Vaccine Effective in Mice

A new vaccine against the main toxin produced by malaria parasites can alleviate some of the most dangerous effects of the disease in mice. If such a vaccine can be fashioned for use in humans, it may provide much needed protection against a disease that kills two million people worldwide each year.

Malaria affects some five to ten percent of the world's population. New drugs to combat malaria are in great demand because the parasites that spread the disease are rapidly becoming resistant to the standard anti-malarial drugs, chloroquine and mefloquine. Although vaccines have been suggested as an alternative to drug therapy for malaria, none has proven effective at countering the disease. One of the keys to developing a successful vaccine lies in finding just the right molecule that can stimulate an immune response against the invading pathogen.

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— **Louis Schofield**

Now, researchers led by Louis Schofield, a Howard Hughes Medical Institute international research scholar at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, have identified a toxin, glycosylphosphatidylinositol (GPI), that contributes to the virulence of malaria in mice, and quite likely in humans. The scientists published their work on GPI in the August 15, 2002, issue of the journal *Nature*.

In 1886, it was proposed by Camillo Golgi that malaria produces a toxin that appears to be associated with the intense periodic fevers caused by the infection, said Schofield. In 1993, we published findings on the properties of GPI, showing that it was a toxin that produces a potent inflammatory response both in cell culture and in mice. That work proposed GPI to be the toxin that Golgi hypothesized more than one hundred years earlier. Our work also led us to believe that GPI constituted an excellent target for a vaccine.

GPI is a glycolipid, a molecule consisting of sugar and fat that is a component of cell membranes. Schofield and his colleagues found that a glycan chain, which is a core component of GPI, was necessary for the molecule to function as a toxin. They reasoned that this glycan would be a good candidate for use in a vaccine.

Schofield's collaborators Peter H. Seeberger and Michael C. Hewitt in the department of chemistry at the Massachusetts Institute of Technology synthesized a pure form of the GPI glycan molecule. Seeberger's elegant synthesis provided for the first time a means to address the problem, said Schofield.

To create a compound that would stimulate an immune response, Schofield and his colleagues coupled the synthetic glycan to large carrier molecules that trigger recognition by the immune system. In initial tests, the researchers found that the anti-GPI vaccine provoked an antibody response in mice. Their results suggested that the GPI from the malaria parasite was sufficiently different from the mouse's own GPI molecules to be recognized as foreign.

The researchers also tested the effects of antibodies from mice immunized with the GPI vaccine on cultured immune cells called macrophages. They discovered that anti-GPI-antibody-treated macrophages showed greatly reduced immune reactions to extracts of the malaria parasite. These experiments demonstrated that GPI itself is a malarial toxin capable of producing inflammation.

In studying the effectiveness of the anti-GPI vaccine, the researchers found that the vaccine alleviated three complications of the disease: blood acidosis, pulmonary edema, and cerebral syndrome, in which the parasite causes clogging of the cerebral arteries. These findings not only show the efficacy of the anti-GPI vaccine in the best available animal model of the disease, but also that GPI is central to the initiation of all these effects, which there was little reason to believe would be causally connected, said Schofield.

According to Schofield, the findings provide additional evidence that GPI is a good candidate for use in a vaccine. We found effects across a wide enough range of processes that I'm very confident that GPI contributes to disease in humans, he said. However, we still have to be cautious about predicting that we can produce a vaccine against GPI in humans.

Over the next few years, Schofield and his colleagues will create a variety of anti-GPI vaccines and test them in other animal models of malaria. This paper represents only a proof of principle, Schofield said. It does not represent an optimized regime on any level, either in terms of synthesis of the GPI molecule or in the carrier protein.

Schofield emphasized that since GPI is an essential molecule in all malaria parasites, a successful anti-GPI vaccine for use in humans could prove permanently effective. We are aiming for a cheap, synthetic molecule that can be conjugated to a carrier protein that is approved for use in humans, he said. And this vaccine can be given to children to produce antibodies very

specific for the parasite GPI and that dont cross-react with human GPI.

The clinical impact of such a vaccine could be major, said Schofield, affording children protection during the first years of life by giving them time to develop acquired immunity to the parasite. Ninety percent of malaria fatalities are in young children, and the long-term hope is that such a vaccine could become a part of standard childhood immunization, he said.