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Mosquito production mooted as fast track to malaria vaccine

Declan Butler, Paris

A leading US researcher is probing an audacious approach to develop a malaria vaccine by cultivating billions of parasites, irradiated to stop them causing disease, in swarms of live mosquitoes.

The approach, which builds on experimental results that are 35 years old, is viewed by other top malaria researchers with a mixture of curiosity, incredulity and admiration.

But its proponent, Stephen Hoffman, founder of Sanaria, a company based in Gaithersburg, Maryland, says he has become disillusioned with the prospects for the current main approach, which uses proteins found on the surface of *Plasmodium*, the parasite that carries the disease. The best of these vaccines has shown only short-term protection in 40–70% of recipients, indicating that a viable malaria vaccine is still years away.

A. D. HOFFMAN & R. C. THOMPSON

Infected mosquitoes bred in captivity could conceivably deliver an effective vaccine against malaria.

So Hoffman is turning to 1967 results from Ruth Nussenzweig's group at New York University, who found that mice could be protected from malaria by being injected with a form of the parasite — known as a sporozoite — extracted from irradiated mosquitoes (R. S. Nussenzweig *et al.* **216,** 160–162; 1967). The sporozoites infect the liver in humans and provoke an immune response, but, because of the weakening effect of the radiation, they don't go on to infect red blood cells or cause malaria.

Stephen Hoffmann: back to basics.

Individually exposing people to thousands of bites by live irradiated mosquitoes is hardly viable for large-scale immunization. But Hoffman claims it should be possible to produce billions of parasites to manufacture a vaccine directly. He intends to breed millions of mosquitoes, grow them on cultures of infected red blood cells, dissect out the sporozoites from the mosquitoes' salivary glands, purify and store them, and then find ways of getting them into people — all under the tough standards of the US Food and Drug Administration.

There is a basis for such a bold project — a re-analysis of published data by various research centres, including the Naval Medical Research Center and the Walter Reed Army Institute of Research, both in Silver Spring, Maryland. This shows that humans exposed to more than 1,000 bites by infected, irradiated mosquitoes develop over 90% protection against subsequent challenges, and that this protection lasts for more than 10 months (S. L. Hoffman *et al. J. Infect. Dis.* **185,** 1155–1164; 2002).

But the logistical problems are formidable. "The barriers have seemed sufficiently daunting that no one has been willing to give it a try," says Thomas Richie, director of clinical trials at the Naval Medical Research Center Malaria Program in Silver Spring.

"It's a long shot," says Adrian Hill, a malaria-vaccine expert at the University of Oxford, UK: "It's worth a try, although the odds are heavily stacked against him."

Hoffman says his work at Celera Genomics on the mosquito genome project helped to convince him that the obstacles could be overcome. He expects to raise $3 million for the project, including a $550,000 grant from the National Institutes of Health.

He will need to produce sufficient numbers of sporozoites, and to store them in a way that retains their ability to infect liver cells. A bite from a mosquito injects around 10–20 sporozoites. So a minimum vaccine dose, equivalent to 1,000 bites, would require at least 10^4–10^5 sporozoites, to ensure that enough living parasites make it to the liver. This is already achievable from one mosquito, says Robert Sauerwein, head of medical parasitology at the University of Nijmegen in the Netherlands, a collaborator of Hoffman's. So one mosquito could produce one vaccine dose.

This assumes that most sporozoites will survive and be immunogenic after storage. If not, many more will be needed. And although mosquitoes inject sporozoites into the blood — an efficient route to the liver — intravenous vaccine injection is not an option. Hoffman thinks that vaccination under the skin should be feasible. But the route to the liver would have to be unusually efficient for this to work.

Hoffman says that with his initial funding he will make sporozoites of clinical-trial quality. If he is successful, a vaccine could be quickly tested in humans in areas of Africa where malaria transmission is high.

The plan is the "best show in town" for malaria vaccines, says Maurice Hilleman, director of the Merck Institute for Vaccinology in West Point, Pennsylvania. "It might even be the only show in town." ■