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Molecule May Be Key to Creating Human-Malaria Resistant Mosquito

Findings published in September issue of Journal of Infectious Diseases

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Malaria is one of the world's deadliest diseases, affecting millions of people each year and resulting in an estimated 1.5 million deaths annually. While malaria transmission has been eliminated within the United States, there has been an increase in malaria cases in recent years, due both to an increasing resistance to anti-malaria drugs and geographic expansion of mosquito populations.

In an effort to prevent the spread of this disease by targeting the mosquito that carries malaria-causing parasites from victim to victim, UCSD School of Medicine researchers have engineered a new molecule that may some day allow for the development of a transgenic human malaria-resistant mosquito. These findings are described in the September issue of the *Journal of Infectious Diseases.*

Anopheles mosquitoes are host to the species *Plasmodium falciparum* -- the species that causes most of malaria-related deaths. In the early 1990s, scientific observation showed that the malaria parasite secretes an enzyme, chitinase, which enables it to invade the mosquito's gut after it ingests a blood meal. Interrupting the chitinase with a chemical inhibitor prevented the parasite from infecting the mosquito.

Joseph M. Vinetz, M.D., associate professor of medicine in UCSD's division of infectious diseases, identified and cloned the gene encoding chitinase and showed, using both vaccine and gene knockout approaches, that the chitinase was critical for the malaria parasite to invade the mosquito stomach. In the present work, Fengua Li, assistant project scientist at UCSD, engineered a single-chain antibody that neutralizes the chitinase, and showed that this molecule is capable of preventing mosquitoes from becoming infected with malaria parasites.

Further, Li, Vinetz and Kailash Patra, also of UCSD, showed that the single-chain antibody blocks both human and chicken malaria parasites from invading mosquitoes. Analysis of the chitinases from malaria parasites of humans, primates, mice and chickens showed that *P. falciparum* is more closely related to a bird malaria parasite than to other human, primate and mouse malaria parasites. Surprisingly, the lethal human malaria parasite appears to have evolved from an ancient malaria parasite of birds or reptiles, rather than from a malaria parasite of mammals.

While previous studies using a mouse malaria parasite have suggested that it would be possible to block parasite infection of mosquitoes, the anti- *P. falciparum* single-chain antibody discovered by the UCSD team "is the first demonstration that we can actually block transmission of a human malaria parasite." Vinetz and Li are working with Dr. Anthony James of the University of California, Irvine, to introduce the anti- *P. falciparum* single chain antipbody gene into mosquitoes to make a transgenic, malaria-resistant Anopheles mosquito.

This finding has the long-term potential to impact malaria transmission, if a genetically modified malaria-resistant mosquito can be created and introduced into the environment.

Vinetz added that there would also be significant issues to be addressed before introducing a genetically altered species into the environment. "But, the global burden of malaria and its impairment of the human condition mandate creative solutions to finding a cure for malaria," he said.

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