

AnAPN1 antigen in transmission-blocking vaccines

THE PROJECT: Exploring transmission- blocking vaccines

The PATH Malaria Vaccine Initiative (MVI) is working in collaboration with the Johns Hopkins Bloomberg School of Public Health (JHSPH) and the Sabin Vaccine Institute (Sabin) to study the feasibility of a vaccine that would fight malaria by interrupting its transmission from mosquito to human. This new collaboration marks MVI's first investment in the transmission-blocking vaccine (TBV) approach. The project aims to produce and test in mice a particular mosquito antigen, *Anopheles* midgut alanyl aminopeptidase (AnAPN1), which has already demonstrated a potential to prevent the two deadliest malaria parasites, *Plasmodium falciparum*, most often found in Africa, and *P. vivax*, which is a significant health threat in Asia and Latin America, from developing in mosquitoes.

With funding from MVI, Sabin will test two different approaches, expression in yeast (*Pichia pastoris*) and expression in bacteria (*Escherichia coli*), for producing higher quantities of the AnAPN1 antigen. This will allow them to determine and evaluate the optimal system for producing a high yield and eliciting proper folding and stability of AnAPN1. The development team will also conduct potency and immunogenicity testing of the antigen.

Scientists at JHSPH will use the antigen produced by Sabin in mouse immunization studies. They will evaluate the ability of different doses of AnAPN1 to block the transmission of a malaria parasite that infects rodents and is biologically very similar to human malaria parasites. The team will also conduct extensive tests designed to detect side effects that could raise safety concerns. This will involve conducting histopathology studies, allowing the researchers to examine the tissue of each immunized mouse to look for signs of disease.

If results from the feasibility study, expected in mid-2011, are positive, the next step would be to consider whether AnAPN1 should undergo further preclinical tests as a prelude to eventual clinical testing.

THE INNOVATION: Blocking the development of the malaria parasite within the mosquito

The parasite that causes malaria is dependent on a life cycle in which it moves from mosquito to human and back to mosquito. A bite from a mosquito delivers the parasite into the human bloodstream via the liver where it proliferates and causes disease. A form of the parasite called the gametocyte circulates within the blood of infected individuals. Malaria transmission perpetuates when mosquitoes bite infected humans and ingest the gametocytes, which eventually mature in the mosquito's gut and migrate to its salivary glands. The mosquito is then poised to deliver the parasite

to the next susceptible individual. A successful TBV employing the AnAPN1 antigen would break this cycle, effectively using the human body to create antibodies that—in the mosquito's gut—would prevent the parasite from completing the development process required for it to infect a human.

Such a vaccine, devoted solely to blocking transmission of malaria, would function differently from a vaccine that protects against clinical disease. A TBV would offer no direct protection against malaria infection to the vaccinated individual. Instead, benefits would be realized over time and throughout the community as the number of infections steadily decline. By preventing the development of malarial parasites within the mosquito, a TBV would also stop the development of secondary infections in humans.

**THE POTENTIAL:
Breaking the cycle of
malaria transmission**

Malaria is one of the world's most urgent public health problems, killing nearly 900,000 people each year, most of them young African children. A vaccine that could block transmission of malaria from mosquitoes to humans would offer another important tool in the fight against the disease.

Supporting the development of this TBV approach is part of MVI's strategy to advance an array of vaccine approaches that have the potential to either halt the malaria parasite or greatly reduce the severity of infection. A successful TBV could break the complex cycle of malaria transmission and help tackle the malaria community's long-term goal of eradication.

THE PATH MALARIA VACCINE INITIATIVE (MVI) is a global program established at PATH through an initial grant from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world. MVI's vision is a world free from malaria. For more information, visit www.malariavaccine.org.

PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act. PATH's work improves global health and well-being. For more information, visit www.path.org.

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SABIN VACCINE INSTITUTE is a nonprofit organization dedicated to reducing human suffering from infectious and neglected diseases. Through its efforts in vaccine research, development, and advocacy, Sabin works to provide greater access to vaccines and essential medicines for millions stuck in pain, poverty, and despair. Founded in 1993 in honor of Dr. Albert B. Sabin, discoverer of the oral polio vaccine, the Sabin Vaccine Institute works with prestigious institutions, scientists, medical professionals, and organizations to provide short- and long-term solutions that result in healthier individuals, families, and communities around the globe. For more information about Sabin's research and commitment, visit www.sabin.org.