

NEWS

The 'Do Unto Others' Malaria Vaccine

Once neglected, research on transmission-blocking vaccines for malaria is gaining new prominence

It used to sound like a far-out idea: a malaria vaccine that would use humans to generate antibodies and deliver them to mosquitoes, with the aim of preventing the insects from spreading the disease. Until recently, such transmission-blocking vaccines (TBVs) had received scant attention. But after Bill and Melinda Gates called for a global effort to eradicate malaria (*Science*, 7 December 2007, p. 1544), TBVs have moved to center stage in malaria vaccine research (see p. 843).

With money no longer the limiting factor, progress is accelerating: A half-dozen TBVs could have a shot at clinical trials sometime in the next 5 years, researchers say. Even so, the scientific and social hurdles remain daunting. Key among them is whether people can be persuaded to get a vaccination that doesn't prevent them from getting sick but instead protects family and neighbors from getting infected. That also raises the bar for an extremely safe vaccine.

Nirbhay Kumar, a molecular parasitologist at Tulane University in New Orleans, Louisiana, has been working to develop a TBV for 28 years, often with little support. But he understands why few funders shared his enthusiasm: With limited resources, it made sense to focus on fighting the disease in humans. Consequently, the few candidate vaccines developed to date attack the parasite during the human stages of its life cycle. The frontrunner, called RTS,S, targets the parasite in the liver stage—when there are hundreds of parasites (see graphic). Other candidates target the blood stage, when there can be trillions of parasites. So far, such vaccines protect people from symptoms of malaria but don't clear all parasites from the blood.

As a result, a vaccinated person could be symptom-free but still be infected and infect others. "You can't eliminate or eradicate [malaria] without addressing the transmission" of the disease, says Kumar. "If we want to completely finish the job, we will need that vaccine," says Christian Loucq, head of the PATH Malaria Vaccine

Initiative (MVI), a nonprofit funded primarily by the Gates Foundation.

Playing the numbers

Antibodies generated by TBVs would be transferred to a mosquito during a blood meal, and they would zero in on the parasite after it enters the insect. That gives them a built-in advantage, says parasitologist Robert Sinden of Imperial College London: Instead of mopping up thousands or even trillions of parasites at once, they have to take out only a handful. The disadvantage? The vaccinated person can still get sick. But a mosquito that bites him or her won't pass the disease to others.

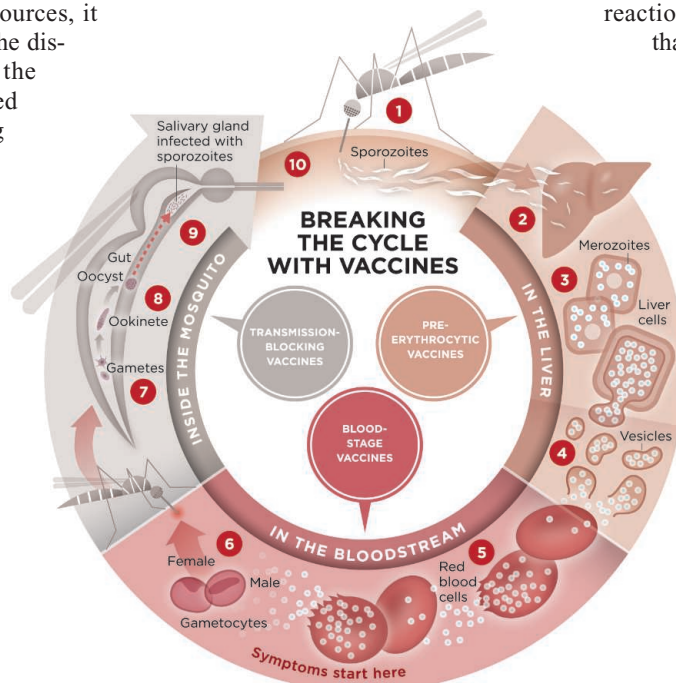
But even with the numbers advantage, developing this new class of vaccines isn't easy. TBV researchers not only have to aim at entirely new targets but they must also overcome many of the same problems that have plagued other malaria vaccines. One of those problems is that *Plasmodium* proteins—the targets of any type of malaria vaccine—are difficult to make in the lab. Usually vaccine producers use bacterial, yeast, or animal cells either to grow the target microbe

directly or to produce recombinant proteins, but the malaria parasite's genome can confound the proteinmaking machinery in these cells. To make matters worse, the antigens must have the right shape to trigger effective antibodies, and getting the recombinant *Plasmodium* proteins to fold correctly has proved difficult. Moreover, because TBVs won't provide direct benefit to the recipient, some say, any TBV with a chance in the real world has to be flawless: absolutely safe, 100% effective, and cheap.

A few teams began testing TBVs in humans a decade ago. The first antigen out of the gate was called Pfs25, named for a 25-kilodalton protein on the *Plasmodium falciparum* ookinete, the fertilized zygote that migrates through the mosquito midgut. Scientists have also tested the analogous protein from *P. vivax*, called Pvs25. (Researchers call both proteins P25 for short.) Like other *Plasmodium* proteins, P25 often failed to fold correctly when expressed in recombinant cells, but animal tests were promising enough to try it in humans.

In initial clinical trials, vaccines based on P25 prompted measurable but weak reactions in healthy volunteers. Based on that experience, malaria experts Yimin Wu and Louis Miller of the National Institute of Allergy and Infectious Diseases in Rockville, Maryland, and their colleagues began a trial in 2005 that combined the antigens with an adjuvant that boosts the body's immune response to a vaccination. The researchers planned to test the vaccine in 72 healthy volunteers.

Initial results showed that some recipients produced antibodies that could block 90% of oocyst development in mosquitoes. But severe reactions in two participants stopped the trial. The combination of adjuvant and antigen was apparently too much for some immune systems, says Anna Durbin, a vaccine expert at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, who coordinated the trial. Sev-



Multiple fronts. Different types of potential malaria vaccines target the parasite at different stages in its life cycle.