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Fragment of Yellow Fever Virus May Hold Key to Safer Vaccine



Image Title: Jan ter Meulen in the field in West Africa - Elisabeth Fichet-Calvet, Museum of National History, Paris

In one of the first molecular studies of the human antibody response to yellow fever, Howard Hughes Medical Institute (HHMI) researchers and their colleagues have found the crucial bit of virus that people's immune systems need to spot and quash this often-fatal re-emerging disease.

The findings may help scientists improve the existing vaccine, which has rare but severe side effects, said Jan ter Meulen, an HHMI international research scholar and associate professor of virology at Leiden University Medical Center in The Netherlands.

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— **Jan ter Meulen**

The group has identified a specific region on one of the viral proteins that elicits an immune response. Antibodies produced by the immune system

interact with this part of the protein, known as a neutralizing epitope, to fight off infection.

To protect people from the disease, yellow fever vaccines must contain this essential fragment of instruction to the immune system, said ter Meulen, senior author of a study published in the July 5, 2005, issue of the journal *Virology* and published early online.

These days, the horror of Ebola or Marburg hemorrhagic fever grabs more attention, but yellow fever is the original viral hemorrhagic fever. It strikes more than 200,000 people a year, mostly in Africa, killing about 30,000 of them, the World Health Organization estimates. No drug treatment is effective against the virus.

Since yellow fever is spread by mosquitoes, much of America has been safe from the disease thanks to control efforts aimed at the insects and a highly effective vaccine that has been available for 60 years. Vaccination is the key strategy for people living in and traveling to tropical Africa, South America, and several Caribbean Islands, where yellow fever is endemic.

In the last 20 years, however, yellow fever has been on the rise, mostly due to the lapse of immunization programs in high risk areas. More recently, serious and potentially fatal side effects from the vaccine have been reported, mainly in elderly persons in northern Europe.

"Yellow fever research was neglected because the vaccine was so effective," ter Meulen said. "Medical science works in cycles. As soon as the problem is solved, the caravan moves on. Once the disease comes back, people realize they are lacking certain information."

To learn more about the immune response and to identify the necessary components of an improved vaccine, ter Meulen turned to survivors of acute yellow fever in the Republic of Guinea in West Africa. Along the war-torn border with Sierra Leone, disruptions in vaccination and medical services led to a large epidemic in 2000. In collaboration with local health authorities, ter Meulen set up a viral hemorrhagic fever laboratory in Conakry to collect and evaluate blood samples from patients.

In people, the mosquito-borne virus incubates for three to six days. Initial flu-like symptoms are followed by a brief remission of up to a day. Then, about 15 percent of people suffer more dangerous complications— jaundice, liver, kidney, and heart damage, and bleeding from the mouth, nose, eyes or stomach. At that stage, ter Meulen and colleagues reported last year in the *Journal of Infectious Diseases*, a person's own immune system, disrupted by its reaction to yellow fever virus infection, may lead to death rather than recovery.

The most recent study was led by Stephane Daffis, a graduate student at Philipps-Universitat in Marburg, Germany. Using blood samples from two yellow fever patients who had recovered, and sophisticated molecular techniques, the researchers generated a library of the millions of specialized

antibodies that made up their immune repertoires.

Then they screened the libraries with a vaccine strain of yellow fever. Four of the antibodies neutralized yellow fever. Genetic analysis showed they all homed in on one particular part of the protein coating the virus. The epitope is called E-71, signifying its address on the envelope protein. Several other amino acids in another section of the folded protein contributed to the neutralization.

Yellow fever virus—and its flavivirus cousins, including dengue and West Nile—look like balls covered by approximately 100 cross-hatched pairs of envelope proteins lying on the surface. The prongs of Y-shaped antibodies against yellow fever likely span the pairs by grabbing the essential epitope on one and the supporting amino acids on the other, ter Meulen speculates. The findings may apply to the whole flavivirus family.

The results confirm and extend similar studies in mice, but the human antibody-virus binding configuration looks more complex, ter Meulen said.

In theory, the crucial antibodies, which have been cloned, could be used for prophylactic protection after suspected exposure, or for therapy, but ter Meulen does not think that pharmaceutical companies are likely to take this approach. More realistically, he said, the findings could help manufacturers design a more consistent vaccine based on recombinant genetic technology, without the potential side effects from variations of the weakened virus strain now grown in fertilized chicken eggs.