

INFECTIOUS DISEASES

Sand Fly Saliva May Be Key to New Vaccine

The saliva of a fly may save human lives--if researchers can transform it into a vaccine. A new study shows that sand flies, minuscule insects that transmit a tropical disease called leishmaniasis, also secrete a protein in their saliva that protects against that disease, at least in mice. The team, led by José Ribeiro of the National Institute of Allergy and Infectious Diseases (NIAID), believes a similar vaccine may one day protect humans.

If true, it would be one of the strangest vaccines ever produced. Almost every existing vaccine directly targets a pathogen--whether it's a virus, a bacterium, or a parasite. Instead, this vaccine goes for one of the vector's proteins. By eliciting an immune response to sand fly saliva, the vaccine is thought to cause local changes in the skin whenever a sand fly bites, making it much more difficult for the parasite *Leishmania* to colonize that area. "It's a very intriguing and promising approach," says epidemiologist Barbara Herwaldt of the Centers for Disease Control and Prevention in Atlanta.

The vaccine would also be a welcome new weapon in the battle against leishmaniasis, says Herwaldt. About 2 million people a year in Africa, Asia, South America, and the Mediterranean come down with the disease, which can take very different forms, depending on which one of about 20 *Leishmania* species is involved. A type called visceral leishmaniasis is deadly when untreated, whereas so-called cutaneous leishmaniasis can cause terrible disfigurements of the face. No good leishmaniasis vaccines exist.

Ribeiro and his colleagues have long studied the saliva of blood-sucking mosquitoes, ticks, and flies for clues to the infection process. These insects have developed a small drugstore of chemicals in their saliva--for instance, blood vessel dilators and anticlotting agents--that help them guzzle blood fast and easily. Components of these cocktails help the insect-borne parasites as well: Without them, some would be unable to cause an infection. Ribeiro and a colleague discovered this in 1988 when they tried to infect mice. Simply injecting the parasite didn't cause disease, but injecting it along with a bit of fly saliva--as would happen in nature--did.



Flying vaccine? A salivary protein from sand flies protects mice from leishmaniasis.

That finding suggested that if the researchers could somehow make the immune system block the action of saliva, that would prevent *Leishmania* infection as well. Indeed, 3 years ago, Ribeiro's team showed that when mice were inoculated with minute amounts of sand fly saliva, they didn't get sick when the parasite was injected along with saliva 2 weeks later..

Of course you can't vaccinate people with insect spit. But in their new study, which appears this week in the *Journal of Experimental Medicine*, Ribeiro's team has produced what may be a workable vaccine. They first isolated the 12 major proteins in the saliva

of *Phlebotomus papatasi*, an important vector of *Leishmania major*, which causes cutaneous leishmaniasis in Africa. They identified one protein, which they called SP-15, that seemed best at protecting mice from infection. Although they don't know what SP-15's function is, they produced a DNA vaccine based on it. Vaccinated mice could eliminate the parasites, while a control group developed large skin ulcers and was unable to clear *Leishmania*.

Ribeiro suspects that vaccinated animals develop a localized immune reaction, called delayed hypersensitivity, when they come into contact with saliva. Immune messenger molecules called cytokines and certain types of immune cells are recruited to the skin site, making it inhospitable for the parasite.

"You prevent the implantation of the organism. ... That's a very interesting new concept in vaccine development," says Antonio Campos-Neto of the Infectious Disease Research Institute in Seattle--and it may work in other insect-borne diseases as well, he says. Even so, Campos-Neto would like to see more evidence of the vaccine's efficacy; for one, the researchers tested the vaccine in a mouse strain that is not as susceptible to leishmaniasis as some others.

One drawback of the strategy may be that about 30 sand fly species are *Leishmania* vectors, each with its own saliva composition, and SP-15 may not work for many of them. But, says Emanuela Handman of the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, "there's nothing to stop people from pulling [saliva] genes from those sand flies, too." And Handman points out one advantage of the saliva vaccine: Because it doesn't target *Leishmania* proteins, it would be very difficult for the parasite to evade it by mutating some of its genes. "This really points the way forward," says Handman.

- Martin Enserink