A Better Bug Spray

Understanding mosquitoes' lust for blood may be the key to curbing some infectious diseases.

Peter Ross

The smell receptor that mosquitoes use to zero in on victims is likely present in other insects, according to Leslie Vosshall.

TO LESLIE B. VOSSHALL, THE TWO MINUTES A MOSQUITO SPENDS FEEDING on human blood are full of suspense: a mini-drama in which the insect, in need of extra protein or iron for egg-laying, risks her own life for the sake of her children. Each turning point in the story—the decision to seek blood, the identification of a victim, the escape from the inevitable swat—ignites Vosshall's deep curiosity about animal behavior.

Vosshall, who became an HHMI investigator in 2008, recently added mosquitoes to her Rockefeller University lab (which has focused primarily on fruit flies) because she wants to help block their ability to transmit infectious disease. Schemes to eradicate the pest do not interest her. Instead, she says, "We want to figure out the blood lust."

"Most of what interests a mosquito about you is how you smell," Vosshall says. "If we can understand that and find a way to interrupt it, then we should be able to solve some problems in infectious disease transmission."

Her team is still equipping the lab for mosquito research—constructing a screened-in zone outside a research room to capture escapees, for example—but Vosshall is well prepared scientifically to find out how and why mosquitoes seek their targets. Her career has focused on elucidating the molecular biology of insect olfaction.

As a postdoctoral fellow in 1993, Vosshall joined HHMI investigator Richard Axel's lab at Columbia University, when little was known about how insects receive and decode olfactory information. Working with fruit flies, she found the first major clue: a large family of genes that encode receptor proteins embedded in the membranes of olfactory neurons. Later, from her own lab at Rockefeller, she mapped how the neurons that express these proteins project into the brain, creating an invaluable tool for correlating odorant receptors to the odor molecules that activate them.

Many of Vosshall's more recent discoveries on insect olfaction have surprised others in her field. "The way insects smell odors is very strange," she says. "Their odorant receptors don't look like any other protein on earth." She showed in 2008 that, unlike mammalian olfactory receptors, which activate signaling pathways inside the cell, insect odorant receptors function as channels that open to let ions flow into the cell when an odor molecule binds. Also unusual, she found, is the existence of an olfactory co-receptor that is present in nearly all insect olfactory neurons and that works in tandem with odorant receptors for specific smells.

That co-receptor, OR83b, is a potential target for what Vosshall describes as an "olfactory confusant," noting that "a protein like OR83b exists in every insect on earth. If we find a chemical that jams this receptor and prevents it from working, we should be able to block the sense of smell in every insect." A fast-acting molecule that blocks OR83b could be sprayed indoors or worn on the body to keep bugs away.

> "The way insects smell odors is very strange. Their odorant receptors don't look like any other protein on earth."
>
> LESLIE VOSSHALL

In fact, her lab showed last year that the common insect repellent DEET works in part by inhibiting OR83b. "It works pretty well, but it's not acting as a universal inhibitor," she says. Her lab is screening chemicals for a more effective alternative.

In the January 9, 2009, issue of the journal *Cell*, Vosshall reported further evidence that insects have their own way of smelling. In search of signaling proteins that help relay olfactory messages to the brain, she and postdoctoral fellow Richard Benton mined the genomes of various organisms in search of genes present in fruit flies and mosquitoes but absent in noninsects. They found a new kind of odor-detecting molecule: receptors that are structurally and functionally distinct from odorant receptors.

It was well known that odorant receptors are found on only about 70 percent of a fruit fly's olfactory neurons. The remaining neurons also send signals to the brain in response to specific odors, but how they did it was "a big, dark secret," Vosshall says.

She and Benton discovered a family of genes that were turned on in olfactory neurons that lacked odorant receptors. The genes' protein products, which they call ionotropic receptors, gave cells the ability to detect specific odors. The researchers had stumbled on a new way that insects detect odors.

Those experiments were done in fruit flies, but the pathway is likely to be common among insects, Vosshall says. It's too soon to say whether targeting that pathway could help them devise a better insect repellent—but it fills in a major gap in knowledge about olfaction and brings Vosshall closer to the complete understanding she is striving for.

Her next step is to find out how identical odors trigger different responses under different conditions. Why, for example, do the cues that signal a human source of blood attract a female mosquito only when she is preparing to lay her eggs? And why does she stop seeking blood once she's had enough?

It's easy to see the practical implications of figuring out how a mosquito's attraction to humans can be switched on and off. In trying to understand the basic biology of olfaction, Vosshall hopes to satisfy her own curiosity about genes and behavior and help conquer some major public health challenges. ■ –JENNIFER MICHALOWSKI