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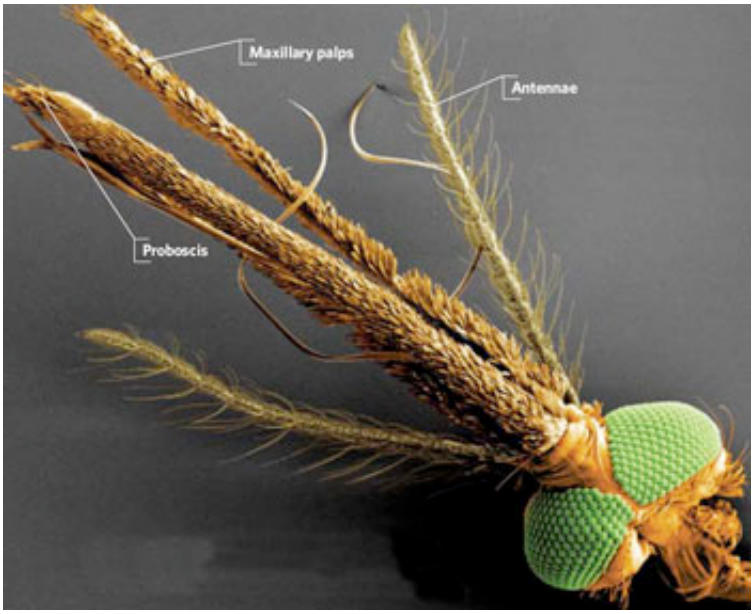
By Brendan Borrell

Smells funny?

Leslie Vosshall thought she had it nailed. Last March, she and two colleagues at Rockefeller University published an elegant series of experiments that seemed to settle the 50-year-old question of how the insect repellent DEET kept mosquitoes at bay (*Science*, 319:1838-42, 2008). "It doesn't smell bad to insects," Vosshall told a reporter from *Science*, "It masks or inhibits their ability to smell you."



Scanning electron micrograph of the head of a female *Anopheles gambiae* mosquito, indicating the olfactory appendages (antennae, maxillary palps and proboscis)

Courtesy of LJ Zwiebel, colorization by Dominic Doyle / Vanderbilt University

It was a public victory for Vosshall's lab and her funder, the Bill & Melinda Gates Foundation. As the gold standard of insect repellents, understanding how and why DEET works so well is critical to designing the next generation of chemicals, which may head off insect-borne diseases such as malaria and dengue fever. Behind the scenes, however, some entomologists expressed puzzlement.

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Laurence Zwiebel of Vanderbilt University (also a Gates' grantee) says he remained circumspect when a reporter asked his opinion of Vosshall's research. Ulrich Bernier of the US Department of Agriculture simply declined to comment. To them, the findings just didn't make sense, given everything they knew about this system.

Leslie Vosshall thought she had it nailed.

In her experiment, Vosshall had measured the response of the mosquito's olfactory neurons to two separate, attractive odors in human breath. Then, she combined each odorant with DEET in a single odor cartridge and noticed a smaller neural response. Vosshall interpreted these data to mean that DEET was blocking the mosquito's olfactory co-receptor.

When Walter Leal's lab at the University of California at Davis made the same observation two years earlier, however, he reasoned that since DEET was highly volatile, it might be preventing other odors from vaporizing and exiting the cartridge—not, as Vosshall believed, blocking the olfactory co-receptor. Using gas chromatography, Leal confirmed his suspicions this year. When he repeated Vosshall's experiment using separate odor cartridges that blended DEET and each attractive odor only at their tips, the mosquito's neural response was no longer diminished. Then, Leal identified a DEET-sensitive odor receptor neuron and showed that mosquitoes avoid passing through a "curtain" of DEET vapors. In September 2008, Leal and Zainulabeuddin Syed published their rebuttal (*PNAS* 105:13598-603, 2008). Their theory: "Mosquitoes smell and avoid the insect repellent DEET."

Leal's paper surprised Vosshall, who first got wind of it when a reporter at *The New York Times* asked for her comment. "I loved our *Science* paper," she says, when I visit her 11th floor office one rainy Friday afternoon in late September. Vosshall is unconvinced by Leal's results, and has been trying to reproduce the effect in her own lab. "Competition in science is good," she says, "It can be difficult when it's a small field, and this is a very small field."

With a lab full of *Drosophila* mutants, Vosshall is a relative outsider in an arena dominated by rubber-boot-wearing field entomologists. ("We're not working on a model system," Zwiebel likes to boast, "We're working on *the* system.") In 1994, Vosshall first cloned the fruit fly's olfactory co-receptor, called OR83b, and in the five years that followed she discovered that it was coupled to odor-specific receptors in every olfactory neuron, convincing her it was a key element in insect repellent strategies. Mutant flies without OR83b couldn't smell anything.

Genomic studies have since shown that this co-receptor is found in insects ranging from mosquitoes to moths, and in 2005, as part of the Gates Grand

Challenge to eradicate malaria, she began looking for a chemical that could block the co-receptors, making humans invisible to insects. Using tissue cultures, she has adopted the philosophy of targeted drug discovery to screen 91,520 compounds from a chemical library, short-listing about 150 that she believes have the potential to be insect "confusants."

In her office, Vosshall pulls up a slide showing the effect of compound #209, which she says is 100-200 times more potent than DEET in blocking OR83b in one particular tissue assay. Part of the controversy, Vosshall says, stems from the fact that DEET is a "messy molecule" with a potential for multiple interactions. Indeed, even Vosshall's skeptics admit the confusant strategy is fundamentally sound. Zwiebel says his unpublished molecular work confirms the existence of confusants, but when it comes to DEET, he and Vosshall aren't willing to budge. "We have agreed to disagree on the DEET story," he says.