Scientists transplant nose of mosquito, advance fight against malaria

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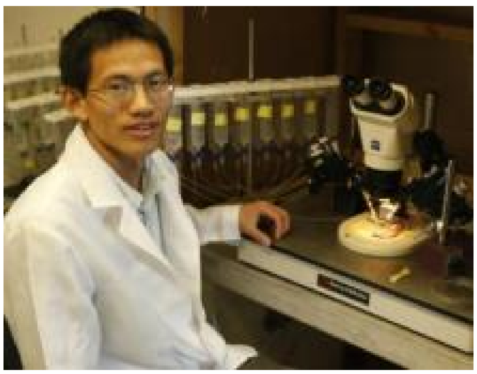

Researcher Guirong Wang sitting at the workstation where he tested the response of mosquito odorant receptors insert into frog eggs to a panel of 110 different odorants. Credit: Steve Green, Vanderbilt University

Scientists at Vanderbilt and Yale universities have successfully transplanted most of the "nose" of the mosquito that spreads malaria into frog eggs and fruit flies and are employing these surrogates to combat the spread of the deadly and debilitating disease that afflicts 500 million people.

The research is described in two complimentary papers, one published this week in the early online edition of the Proceedings of the National Academy of Sciences and the other which appeared online Feb. 3 in the journal *Nature*.

The mosquito's "nose" is centered in its antennae, which are filled with nerve cells covered with special "odorant receptors" that react to different chemical compounds. The insect ORs are comparable to analogous receptors in the human nose and taste buds on the tongue.

"We've successfully expressed about 80 percent of the Anopheles mosquito's odorant receptors in frog's eggs and in the fruit fly antennae," says Laurence Zwiebel, professor of biological sciences at Vanderbilt, whose lab performed the frog egg transplantation. The fruit-fly (Drosophila melanogaster) work was done in the laboratory of John Carlson, Eugene Higgins Professor of Molecular, Cellular and Developmental Biology at Yale.

Both accomplishments are part of a five-year project supported by the Grand Challenges in Global Health Initiative funded by the Foundation for NIH through a grant from the Bill & Melinda Gates Foundation with the goal of producing novel ways to inhibit the spread of malaria. Scientists from the Wageningen University in the Netherlands, the African Insect Science for Food and Health Institute in Kenya, Ifakara Health Institute in Tanzania and the Medical Research Council Laboratories in the Gambia are also participating in the project.

Previously, scientists have used frog eggs to study the olfactory receptors of moths, honeybees and fruit flies. DNA that encodes insect receptors are injected into a frog egg and given sufficient time to produce and localize proteins. As a result, the surface of the egg is covered with the mosquito odorant receptors. An engineered egg is placed in a voltage clamp system and an odorant is dissolved in the buffer solution in which the egg is floating. If the mosquito receptors react to the compound, the electrical properties of the egg change in a measurable fashion.

"The frog egg system is relatively rapid, highly sensitive and allows us to do very precise measurements of odorant response," says Guirong Wang, a senior research associate in the Zwiebel lab who was the lead author on the PNAS study and carried out several thousand egg/odorant recordings. "However, we call this a medium throughput system because, while it is relatively quick to set up, we have to make the odorant solutions by hand, which goes relatively slowly."

By comparison, Yale's Drosophila system is a somewhat lower throughput system because it takes about three months to engineer a fruit fly with a mosquito odorant receptor in its antennae. The system, originally developed in the Carlson lab, uses mutant flies that are missing an odor receptor. Allison Carey, a graduate student in the Yale lab, systematically inserted mosquito genes into fruit flies one at a time so that a mosquito odorant receptor was expressed in place of the missing receptor. Although the method is slightly slower than the frog egg approach, it has some distinct advantages: Most notably it responds to volatilized odorants so it works with compounds that don't dissolve readily in water. It is also effective in detecting chemicals that inhibit receptors rather than exciting them.

"Both teams used the same set of 72 Anopheles odorant receptors and tested them using the same panel of 110 odorants," says Wang. The Vanderbilt team got responses from 37 of the odorant receptors in the frog eggs while testing 6,300 odorant-receptor combinations. "The results of the two systems were quite similar. There were only a few small differences."

Both studies found that most mosquito receptors are "generalists" that react to a number of different odors while a few are "specialists" that respond to a single or small number of odors. In some cases, the researchers found that a single odorant triggers several receptors while in other cases receptors are specifically tuned to unique compounds. In particular, they found 27 Anopheles receptors that respond strongly to compounds in human sweat.

"We're now screening for compounds that interact with these receptors. We call those that do BDOCs (behaviorally disruptive olfactory compounds)," Zwiebel says. "Compounds that excite some of these receptors could help lure mosquitoes into traps or repel them away from people while others that block receptor activity may help mask people. Ultimately we are looking for cocktails of multiple compounds that demonstrate activity in the field."

The project has already developed and patented a blend of BDOCs that is more attractive to mosquitoes than humans and has also identified several repellant BDOCs. It is currently in product development discussions with several private sector companies.

Provided by Vanderbilt University

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