Deadly parasite's rare sexual dalliances may help scientists neutralize it

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For years, microbiologist Stephen Beverley, Ph.D., has tried to get the disease-causing parasite *Leishmania* in the mood for love. In this week's *Science*, he and colleagues at the National Institutes of Health report that they may have finally found the answer: Cram enough *Leishmania* into the gut of an insect known as the sand fly, and the parasite will have sex.

Some strains of the parasite are deadly and kill hundreds of thousands of people annually in developing countries. Offspring of the parasite's dalliances may hold the genetic key to neutralizing it. The achievement could be an important step toward identifying the genes that determine the parasite's deadliest characteristics. That in turn could enable the development of new treatments for those infections.

"The idea would be try to cross the mild strains with more harmful strains, and look to the descendants to see which retains the ability to cause severe infection," says Beverley, Ph.D., the Marvin A. Brennecke Professor and head of Molecular Microbiology. "By tracking which portions of the deadly parent's genetic material consistently pass on to deadly descendants, we should be able identify the segments of the genome that control the parasite's ability to cause severe infection."

Beverley's co-senior author on the report is David Sacks, Ph.D., a National Institutes of Health researcher who specializes in the sand fly and parasite immunology. Infection with the *Leishmania* parasite, or *Leishmania*sis, is mainly spread by sand fly bites and is a major public health problem in Asia, Africa, the Middle East and other parts of the

developing world. Symptoms include large skin lesions, fever, swelling of the spleen and liver, and, in more serious forms of the disease, disfigurement.

The most severe form of *Leishmania*sis, a condition sometimes called black fever, is fatal if left untreated and is estimated to kill more humans than any other parasite except *Plasmodium falciparum*, the malaria parasite.

Like many microorganisms, *Leishmania* can reproduce either by cloning or through the creation of descendants containing genetic material from more than one parent—the microbial equivalent to sex. For now, researchers can only detect sex in *Leishmania* by its final product: a descendant with an unusual mixture of genes.

After more than 20 years of trying to get *Leishmania* to have sex in culture dishes, never knowing for certain if the parasite ever did reproduce sexually, Beverley and Sacks recently found the key was getting enough parasites into the sand fly. Natalia Akopyants, Ph.D., instructor in molecular microbiology at Washington University, detected the new hybrid parasites through genetic analysis.

"Our theory, which is not proven yet, is that it's a numbers game," Beverley says. "Every time we got enough parasites into the fly, we saw sexual crossing. If we didn't get good infections, we saw no evidence of sex."

The scene inside the sand fly is no microbial bacchanal: nearly all of the parasites reproduce via cloning instead of sex. The mechanics of sexual reproduction in *Leishmania* are still unclear. It's not known, for example, if they produce some type of microbial gametes that, like the egg and sperm of higher organisms, contain half of the normal complement of genes from each parent and combine to form a genetically whole

organism.

Beverley hopes to develop a technique to highlight *Leishmania* when it's reproducing sexually so researchers can better understand what happens during sex and more quickly identify the factors in the fly gut that prompt it.

"If we can find a way to make the parasites that are in flagrante delicto light up, that might give us some clues as to what songs we have to sing to them to get them to mate in a culture dish," he says.

Beverley notes that the new study would have been impossible without the Sacks lab's expertise in sand flies, but he would like to find a way to take the sand fly out of future genetic experiments and have *Leishmania* breed in culture.

"There are important interactions going on between the sand fly and the parasite in nature that we need to understand, and as a world leader in this area the Sacks labs' capabilities are going to be essential for that," he notes. "But for the purpose of finding the genes that make *Leishmania* dangerous, we would just as soon eliminate the time and the expense of breeding within the sand fly."

More information: Akopyants NS, Kimblin N, Secundino N, Patrick R, Peters N, Lawyer P, Dobson DE, Beverley SM, Sacks DL. Demonstration of genetic exchange during cyclical development of Leishmania in the sand fly vector. *Science*, April 10, 2008.

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