Podcast Interview: Marcelo Jacobs-Lorena

PNAS: I’m Sandeep Ravindran, and welcome back to Science Sessions. Malaria is one of the deadliest infectious diseases, affecting more than half of the world’s population and killing more than a million people each year. A recent PNAS study described an innovative approach that could help curb the disease’s spread. In the study, Johns Hopkins University professor Marcelo Jacobs-Lorena genetically engineered a symbiotic bacterium that normally lives in mosquito guts, the same place where the malaria parasite *Plasmodium* is at the most vulnerable stage of its mosquito lifecycle. The bacteria were modified to secrete substances that are toxic to *Plasmodium*, significantly inhibiting the parasites’ development. The technique is still being refined for use in the field, but Jacobs-Lorena hopes to eventually be able to use this approach to curb malaria transmission worldwide. Jacobs-Lorena spoke to PNAS over the phone, and describes how he began developing methods to block malaria transmission.

Jacobs-Lorena: We have been working with the interaction between the parasite and the mosquito vector for 15-20 years, and we found a small peptide that can block the cycle of the parasite in the mosquito. And so we engineered a gene that expresses the small peptide, and indeed, this transgenic mosquito was highly resistant to the parasite. So that was a good news. So the next step would be to introduce that blocking gene into mosquito populations in the field, and that turned out to be quite a difficult task. You would have to give the mosquito that carries this gene an advantage over the mosquitoes that are in the field, and that is not easy to do.

PNAS: Jacobs-Lorena decided to try an alternative strategy, using a symbiotic bacterium called *Pantoea agglomerans* that lives in the mosquito gut.

Jacobs-Lorena: Then we thought that the mosquitoes, like us, they have bacterial flora in their gut. And the parasite also starts development in the mosquito midgut where the bacteria are. So the idea was instead of engineering the mosquito to produce those interfering substances, engineer the bacteria to do that. And we tested it and indeed it worked. We perfected this approach by working with the bacterium that lives normally in the mosquito midgut, and having it produce a number of different interfering substances, and we found among them some that are highly inhibitory, up to 98%. The other advantage of this approach is that when the mosquito takes a blood meal, the blood has a lot of nutrients, so the number of bacteria in the midgut increases dramatically. So the more bacteria you have, the more interfering substance you make, and so that helps as well.

PNAS: The researchers still had to figure out a way to get the bacteria into mosquitoes in the field.

Jacobs-Lorena: What we found out is that there is another bacterium, that when you feed to the mosquito, is able to colonize the ovaries of the mosquito, and when the mosquito lays an egg, the bacteria sort of hitches a ride and attaches to the egg, and is laid into the water, and the larvae that hatches from this egg, they will ingest the bacteria. And we also found that if you feed this bacteria to males, when they mate with
the females, they transfer this bacteria to the females. So we are now putting our hopes in this new kind of bacteria.

**PNAS:** While Jacobs-Lorena hopes to eventually test the approach in the field, he currently simulates field conditions to study its effectiveness.

**Jacobs-Lorena:** The biggest concern is that we are talking about introducing genetically-modified organisms in nature, and that can have some obstacles from the point of view of getting regulatory approval, and approval of the local population. So in the meanwhile, we are planning some semi-field experiments in so-called “malaria spheres”, which are essentially large enclosed environments that completely simulate the field conditions, where they can maintain large populations of mosquitoes. If we can show that under natural conditions the bacteria spread, that would be a big step forward.

**PNAS:** The bacterium is effective against multiple plasmodium strains and is well adapted to multiple mosquito species, and Jacobs-Lorena says it could play a major role in the fight against malaria.

**Jacobs-Lorena:** If those two predictions occur, that it adapts to any mosquito species and interferes with any parasite species, then it would be sort of a universal weapon against malaria.

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