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ANTIMICROBIALS

Arming symbionts with antimalarials

> “the tested proteins reduced oocyst numbers in two different mosquito species”

As the frequencies of mosquito insecticide resistance and parasite drug resistance continue to rise, alternative strategies to curb the emergence and spread of malaria are urgently needed. Previous efforts have focused on genetically modifying the mosquito vector to resist infection with *Plasmodium* spp.; however, this has been difficult to achieve owing to technical challenges. Now, Wang *et al.* report the engineering of a mosquito symbiont to secrete anti-*Plasmodium* effector proteins and show that this strategy effectively impedes parasite development in the insect.

During their life cycle, *Plasmodium* spp. transition through various developmental stages in vector mosquitoes, where differentiation from ookinetes to oocysts occurs in the midgut. This is considered to be the most vulnerable stage of development as it is accompanied by a population bottleneck, which sees a severe drop in the number of parasites. The bacterium *Pantoea agglomerans* is a common member of the mosquito midgut microbiota, and its numbers rapidly expand after ingestion of a blood meal. Thus, by introducing transgenes encoding anti-*Plasmodium* effectors into *P. agglomerans*, the authors aimed to maximize exposure of the parasite to these inhibitory proteins at a time and place at which it is most sensitive to killing.

Plasmids encoding one of a range of effector proteins were individually transformed into *P. agglomerans*, along with a second plasmid encoding the *Escherichia coli* haemolysin A system, which facilitated secretion of the effectors from the engineered bacteria. To examine the effectiveness of this strategy *in vivo*, mosquitoes were administered with recombinant bacteria and later fed a blood meal containing *Plasmodium falciparum*. Oocyst counts taken 8 days after infection were used to evaluate the inhibitory action of each effector protein.

Although all of the tested effectors reduced oocyst numbers, a scorpion antimalaria lytic peptide (scorpine) and a fusion peptide composed of a chitinase propeptide and four copies of the *Plasmodium* enolase–plasminogen interaction peptide demonstrated the most potent inhibition and reduced oocyst formation by ~98%. Furthermore, the infection prevalence (the proportion of mosquitoes carrying oocysts) was reduced by up to 84% when scorpine-secreting bacteria were present. Finally, the authors found that each of the tested proteins reduced oocyst numbers in two different mosquito species and that they were also active against the rodent parasite *Plasmodium berghei*, indicating that this strategy may be a universal solution for the control of malaria.

These data demonstrate how the microbiota can be manipulated to provide a powerful weapon against pathogens. However, technical obstacles, such as devising an efficient strategy for the colonization of wild mosquitoes with engineered symbionts, as well as controversies surrounding the release of genetically modified organisms into the environment, remain to be addressed.

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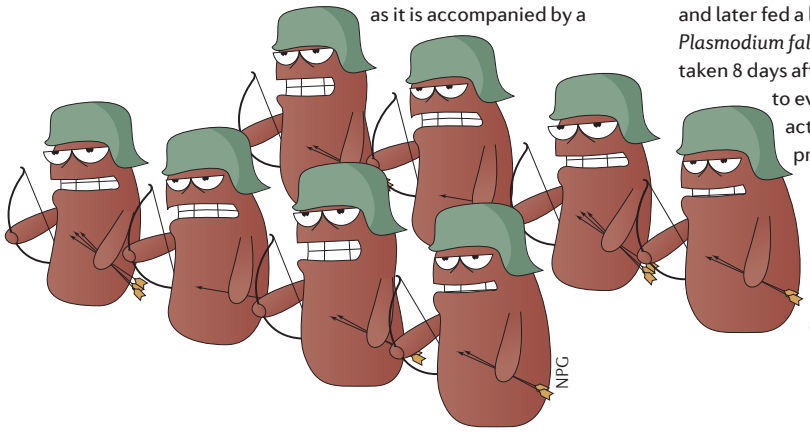

ORIGINAL RESEARCH PAPER Wang, S. *et al.* Fighting malaria with engineered symbiotic bacteria from vector mosquitoes. *Proc. Natl Acad. Sci. USA* 16 Jul 2012 (doi:10.1073/pnas.1204158109)