New antibody insecticide targets malaria mosquito

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Credit: CDC

Malaria is a cruel and disabling disease that targets victims of all ages. Even now, it is estimated to kill one child every minute. Recent progress in halting the spread of the disease has hinged on the use of insecticide-treated bed nets and spraying programmes that target the insect that spreads the disease, the African malaria mosquito (*Anopheles gambiae*). However, the insects are fighting back, developing resistance to

insecticides such as pyrethroid that control their numbers, forcing Brian Foy and Jacob Meyers from Colorado State University to think of alternative control strategies. Wondering if they could defeat the mosquitoes by developing a new insecticide, the duo decided to try to make blood meals toxic for mosquitoes. They decided to test whether antibodies targeted at a key component of the malaria mosquito's nervous system could be fed to the insects in a blood meal to kill them.

The scientists publish their discovery that these antibodies are toxic and kill malaria mosquitoes in *The Journal of Experimental Biology*.

Identifying a glutamate gated chloride channel (the mosquito glutamate gated chloride channel - AgGluCl), which is an essential component of the insect's nervous system, to be the target of their novel strategy the duo decided to generate antibodies that specifically targeted a portion of the protein that is exposed on the surface of nerves to try to exterminate the disease carriers. However, Meyers admits that the strategy was risky. 'Antibodies against a single mosquito antigen have never been shown to have mosquitocidal properties before and the majority of previous research had focused on midgut antigens, while we were targeting a neuronal antigen expressed only in tissues found outside of the midgut', he says.

Injecting rabbits with a tiny portion of the surface of the AgGluCl protein channel, Meyers waited for the rabbits' immune systems to kick in and begin producing antibodies tailored to the channel. Then he collected the antibodies, mixed them with fresh blood and fed the tasty mixture to malaria mosquitoes and two other disease carrying species; yellow fever mosquitoes and West Nile virus mosquitoes.

Frustratingly, neither the yellow fever nor West Nile virus mosquitoes responded to the spiked blood. However, significant numbers of the malaria mosquitoes expired after the blood/antibody cocktail, with the

highest antibody doses killing over 90% of the insects within a day. And when Meyers and Meg Gray tested why the yellow fever and western encephalitis mosquitoes had been immune to the antibody snack, they found that the antibodies could not pass across the yellow fever- or West Nile virus mosquitoes' guts into the hemolymph, while the antibodies passed into the haemolymph of the malaria carrying mosquitoes with ease.

Intrigued by the antibodies' mode of action, Meyers fed the insects a blood meal laced with the antibodies and a lethal dose of Ivermectin, an insecticide that also targets the AgGluCl protein channel, and monitored their survival to find out more about how the antibody may destroy the insects. Remarkably the insects fed Ivermectin with the antibodies survived much better than insects fed Ivermectin alone. 'We believe that Ivermectin is able to bind to AgGluCl, but the antibody keeps the channel from opening and becoming active', says Meyers.

Having shown that antibodies targeted to the glutamate gated chloride channel in blood meals can be effective insecticides, Meyers and Foy are keen to find out if antibody-laced blood meals are equally deadly in real life. 'The next step... is to immunize cattle against the AgGluCl antigen and directly feed *An. gambiae* on the immunized cattle in the lab', explains Meyers. And if the strategy proves successful, Meyers envisages a large scale cattle immunisation program as part of a combined attack on the parasite. 'Cattle are a major blood meal source for multiple malaria vectors,' he says, explaining that any malaria-harbouring mosquito that consumed blood carrying the toxic antibodies during the malaria parasite's incubation period would die, disrupting transmission of the disease and offering hope of a malaria-free future for generations to come.

More information: Meyers, J. I., Gray, M. and Foy, B. D. (2015). Mosquitocidal properties of IgG targeting the glutamate-gated chloride

channel in three mosquito disease vectors (Diptera: Culicidae). J. Exp. Biol. 218, 1487-1495.