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Drug treatment has profound effect on cerebral malaria in mice

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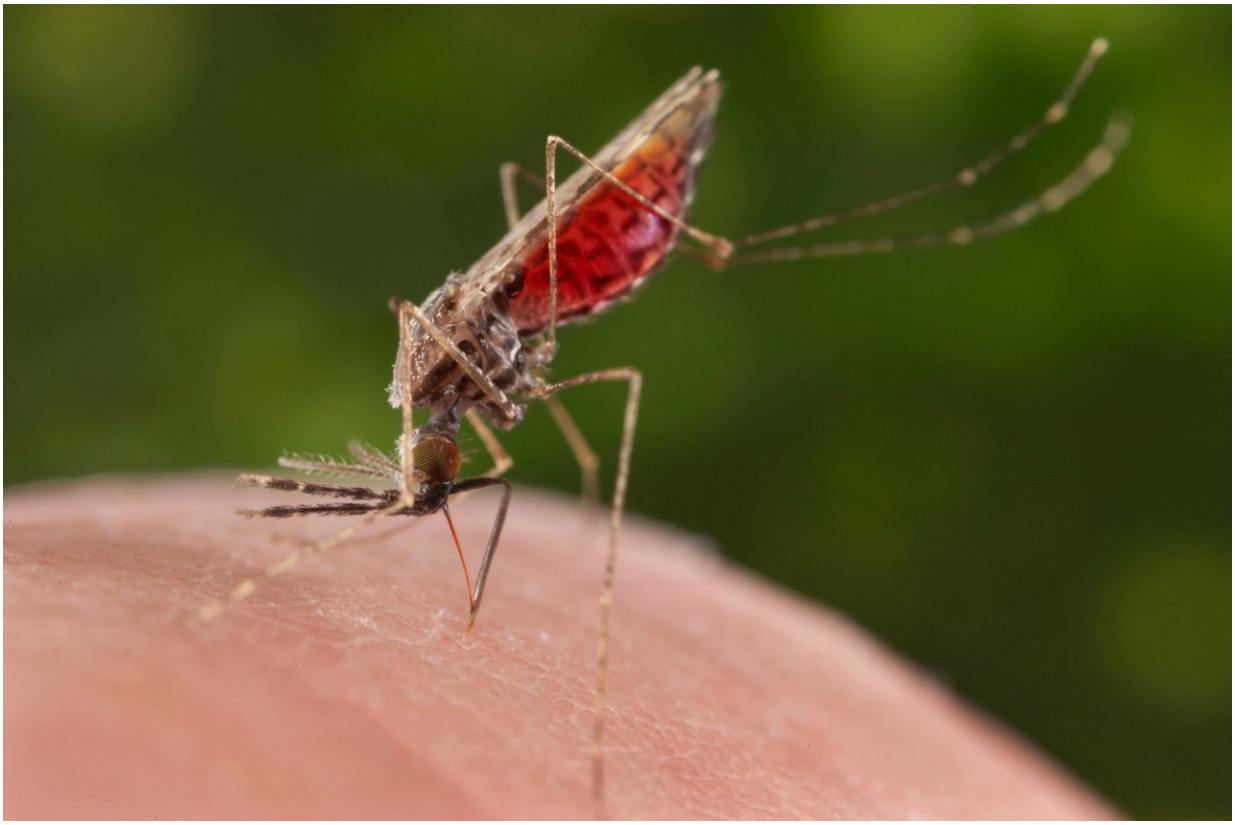

Credit: University of Manchester

A potentially new way of treating cerebral malaria has been discovered by scientists at the Universities of Manchester and Glasgow, in a study using mice.

The authors found that inhibiting a complex called the inflammasome, at the same time as delivering anti-malarial drugs, reduced mortality from experimental cerebral malaria in mice.

The research, published in *PNAS* and funded by the Medical Research Council, also shows that animals treated with inflammasome inhibitors and anti-malarial drugs had significantly reduced levels of cerebral pathology and signs of neurological impairment, compared with mice treated only with anti-malarial drugs.

Though the team are yet to trial the drug on humans, the research constitutes a significant breakthrough in the fight against malaria, which according to the World Health Organisation kills 438, 000 people every year.

"Cerebral malaria is so deadly because there are no early symptoms; it's often hard to spot until it's too late," said Dr. Kevin Couper from The University of Manchester.

"We were particularly interested in looking at why anti-malarial drugs, the only current treatment for the condition, do not promote optimal recovery from cerebral malaria, as well as developing new therapies. So, we were delighted when we discovered some of the biological processes involved."

After sequencing the RNA in brain cells of mice, the team realised that recovery associated with experimental cerebral malaria was regulated by a family of genes involved in controlling the immune response within the brain.

When the product of one of the genes called IL33 was given anti-malarial drugs, mortality in mice went from 20% to 0% and pathological features in the brain such as haemorrhage, blocked vessels, leakage and

impaired neuronal signalling were also significantly reduced.

The results suggested that IL33 was important for inhibiting the inflammasome, and when the team used an inflammasome inhibitor alongside anti-malarial drugs to treat experimental cerebral malaria they got the same result as treatment with IL33.

Dr. Couper said: "This is an extremely promising area of research and we are excited that there is now a genuine way forward for researchers to work on.

"But it's clear that mice are not humans and our next stage will be to check if this dysregulation in the IL-33-inflammasome pathway occurs in people who have cerebral malaria and influences their recovery, and we are starting to do that with partners in Africa."

Prof David Brough, from The University of Manchester, was also on the research team. He said: "The identification of the inflammasome in experimental cerebral malaria highlights it as an important therapeutic target and complements our ongoing research to develop more effective inhibitors for use in treating inflammatory disease."

Plasmodium falciparum, is the species of parasite that causes malaria, and the cerebral malaria complication, in humans. The parasite is spread by mosquitoes when the mosquito, a female Anopheles mosquito, feeds.

The paper, "Targeting the IL-33-NLRP3 axis improves therapy for experimental cerebral malaria," is published in *PNAS*.

More information: Patrick Strangward el al., "Targeting the IL33–NLRP3 axis improves therapy for experimental cerebral malaria," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1801737115