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Slamming the brakes on the malaria life cycle

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Scientists have discovered a new target in their fight against the devastating global disease 'malaria' thanks to the discovery of a new protein involved in the parasite's life cycle.

The research has uncovered a vital player in the sexual phase of the malaria parasite's reproduction which could prove an effective target for new treatments to stop the disease in its tracks.

The scientists from The University of Nottingham's School of Biology, with collaborators from the Universities of Leicester, Oxford, Imperial College London and Leiden in the Netherlands, have just published the results of their work in the journal *PLoS Pathogens*.

Malaria is a devastating global disease with several hundred million clinical cases and just under a million people die from it every year. The disease is caused by an infection of the red blood cells with a tiny parasite called a Plasmodium, of which there are four important species. These organisms are carried from person to person by the *Anopheles* mosquito. When it bites an infected person, the mosquito sucks up blood containing the parasite, which may then be passed on to the mosquito's next victim.

Dr David Guttery, lead scientist of the paper and part of Dr Tewari's group from the University of Nottingham's Centre for Genetics and Genomics in the School of Biology said:

"The malaria parasite is a complex organism and to understand how it

multiplies is crucial to stopping its transmission. Our study has identified a cell-division cycle gene in the malaria parasite and its role in the development of male sex cells and is hence a good candidate for putting the brakes on its development. We have shown that by deleting this gene, male gametes cannot form and burst out of their host cell (a process called exflagellation). Blocking the formation of these cells can be an important strategy in the prevention of malaria transmission from mosquito to mammalian hosts".

The protein that has been identified is called CDC20 and plays a part in the cell division cycle of the malaria parasite *Plasmodium berghei* which infects mice and rats. This gene has been shown to have an important role in cell division in many organisms, but up to now nothing has been known about its function in the malaria parasite. The new study provides the first description of the role of CDC20 in *Plasmodium* cell division and in the development of the malaria parasite's male sex cells (microgametes), which are essential for parasite transmission between humans and the mosquito carrier. The scientists have discovered that the absence of this gene stops the male sex cell from bursting out of its host cell and fertilising a female cell as they are arrested in their cell division.

The sexual stage of the malaria parasite's life-cycle occurs within the mosquito after it has fed on malaria-infected blood. This activates the parasite's sexual phase and during this period, the male sex cell precursor (microgametocyte) rapidly replicates it DNA and produces 8 male sex cells (gametes). These gametes then burst out of the microgametocyte in a process called exflagellation and seek out a female sex cell to fertilise. By blocking the process of exflagellation, the team have identified a way of slamming the brakes on malaria transmission.

The team of researchers were from the Centre of Genetics and Genomics at The University of Nottingham, the University of Oxford, Imperial College London, Leiden University, the University of Leicester

and the MRC National Institute for Medical Research funded by the MRC, Wellcome Trust, and EviMalar.

The group at Nottingham has previously uncovered other major players in the life cycle of the malaria parasite. More details on these can be found in earlier media releases 'Stopping the spread of malaria' and 'Malaria research begins to bite'.

More information: *PLoS Pathogens*, DOI:10.1371/journal.ppat.1002554

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