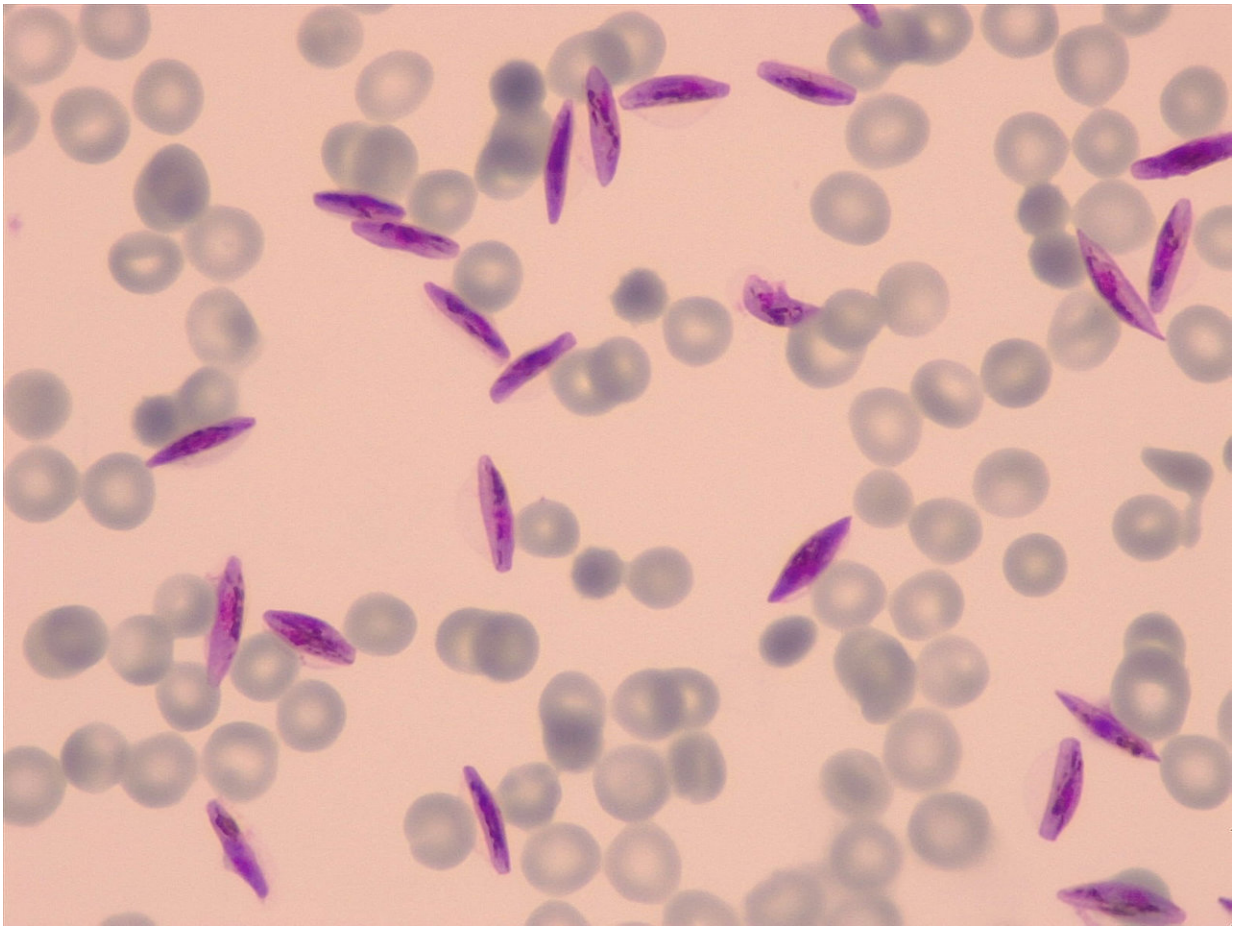
New understanding of parasite biology might help stop malaria transmission

March 15 2018



Gametocytes of *p. falciparum* in human red blood cells. Credit: Eva Hitz/Swiss TPH

Malaria parasites multiply asexually in the human bloodstream, thereby causing chronic infection and all the complications associated with this devastating disease. During each round of multiplication, a small proportion of parasites develop into non-dividing gametocytes instead. Gametocytes are infectious to mosquitoes and are therefore the catalyst for transmitting malaria to other humans. Understanding how malaria parasites control the switch to gametocyte production is central to support the development of therapeutic interventions that could block malaria transmission.

How malaria parasites turn the switch

Whether a parasite continues to multiply or develops into a gametocyte is controlled by a molecular switch. A recent publication in Cell demonstrated that this switch responds to a lipid molecule present in human blood: lysophosphatidylcholine (LPC). Under high LPC concentrations, parasites multiply, consuming LPC to build new membranes. When LPC concentrations drop, as they do during acute infections, parasites convert into gametocytes to secure their transmission to the next human host.

Researchers at the Swiss Tropical and Public Health Institute (Swiss TPH) have now identified a parasite protein (GDV1) that plays a crucial role in activating the gametocyte conversion switch. "GDV1 basically ignites a process that reprograms gene expression in the parasite such that gametocyte development occurs," said Till Voss, corresponding author of the study and Head of the Malaria Gene Regulation Unit at Swiss TPH.

The study in *Science* further shows that GDV1 is only produced in parasites destined to develop into gametocytes. In multiplying parasites, an inhibitory molecule prevents expression of GDV1. "We were amazed to observe that after targeted disruption of this inhibitory molecule using

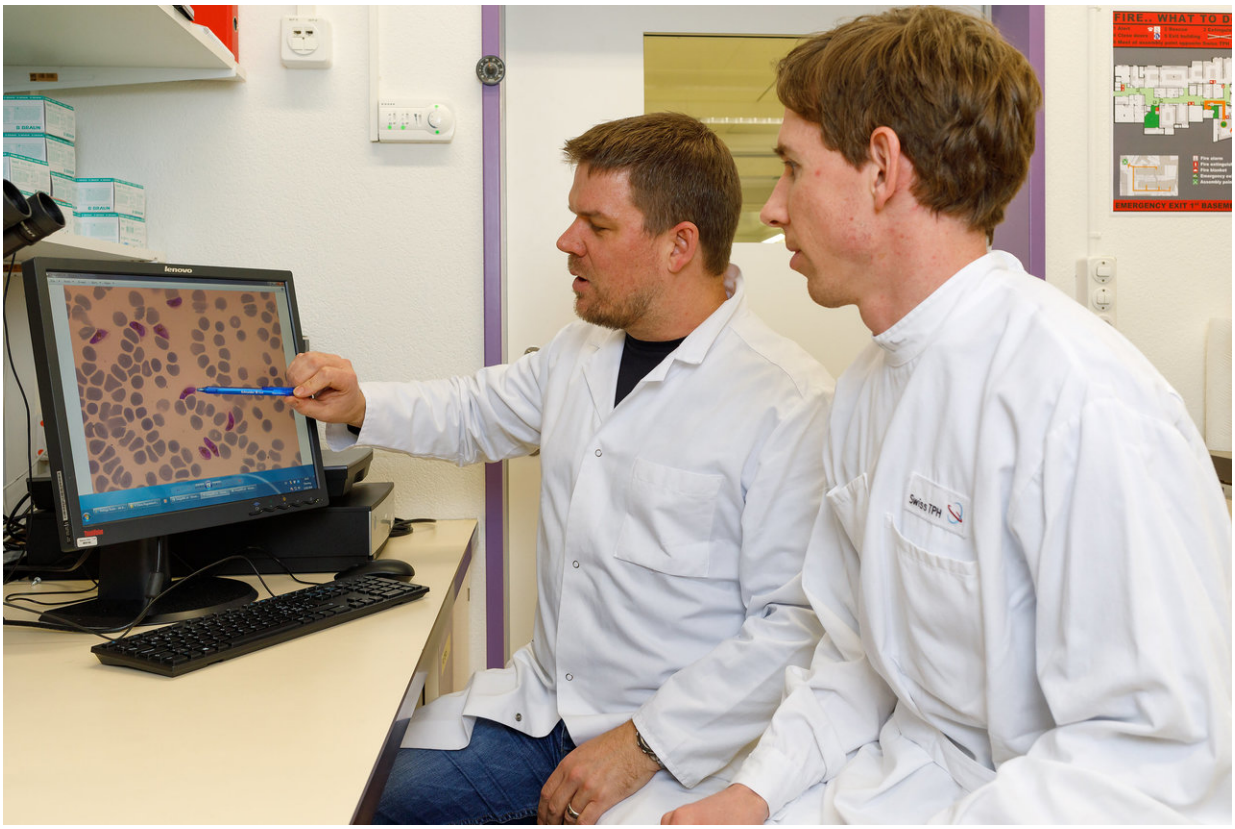
CRISPR-Cas9 technology, all parasites expressed the GDV1 protein," said Michael Filarsky, first author of the study and scientist at Swiss TPH. Another important finding of this study is that GDV1 production is likewise inhibited by LPC. "This is exiting. We are onto the molecular pathway that transports an environmental stimulus into the parasite to activate gametocyte development," concludes Voss.

Michael Filarsky, first author of the study, in a Swiss TPH laboratory. Credit: Joachim Pelikan/Swiss TPH

"Fundamental knowledge and a new tool for future research"

Drugs and vaccines that target gametocytes are urgently needed to reach

the declared aim of eliminating and eradicating malaria. "Although our study does not offer immediate solutions for novel therapies, it sheds new light on the mechanisms responsible for the production of gametocytes," said Till Voss. "If we can block this mechanism or eliminate gametocytes altogether, we might get an important step closer to interrupting malaria transmission."



Till Voss (left), corresponding author, and Michael Filarsky, first author, in Swiss TPH laboratory. Credit: Joachim Pelikan/Swiss TPH

The new knowledge also allows Swiss TPH scientists to produce high quantities of gametocytes in the laboratory. "Research on gametocytes is hampered by the fact that they usually only arise in very small numbers,"

said Michael Filarsky. "We are now able to engineer genetically-modified parasites that deliver enormous quantities of gametocytes. We predict that these parasites will be useful not only for future basic research, but also for applied research in this area."

The study results will be published on 16 March 2018 in *Science*.

More information: "GDV1 induces sexual commitment of malaria parasites by antagonizing HP1-dependent gene silencing" *Science* (2018). science.sciencemag.org/cgi/doi … 1126/science.aan6042

Provided by Swiss Tropical and Public Health Institute