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Viagra to prevent transmission of the malaria parasite?

By increasing the stiffness of erythrocytes infected by the causal agent of malaria, Viagra favors their elimination from the blood circulation and may therefore reduce transmission of the parasite from humans to mosquitoes. This astonishing discovery, made by scientists from the CNRS, INSERM, Université Paris Descartes – at the Institut Cochin – and the Institut Pasteur, working in collaboration with a team from the London School of Hygiene and Tropical Medicine, could lead to a treatment to reduce the spread of malaria within a population. Their work is published in *PLOS Pathogens* on 7 May 2015.

Plasmodium falciparum, the parasite that causes malaria, has a complex developmental cycle that is partially completed in humans and partially in the anopheline mosquito. Treatments for malaria target the asexual forms of this parasite that cause symptoms, but not the sexual forms transmitted from a human to a mosquito when it bites. Eradication of this disease thus necessitates the development of new types of treatments against sexual forms of the parasite in order to block transmission and thus prevent dissemination of the disease within the population.

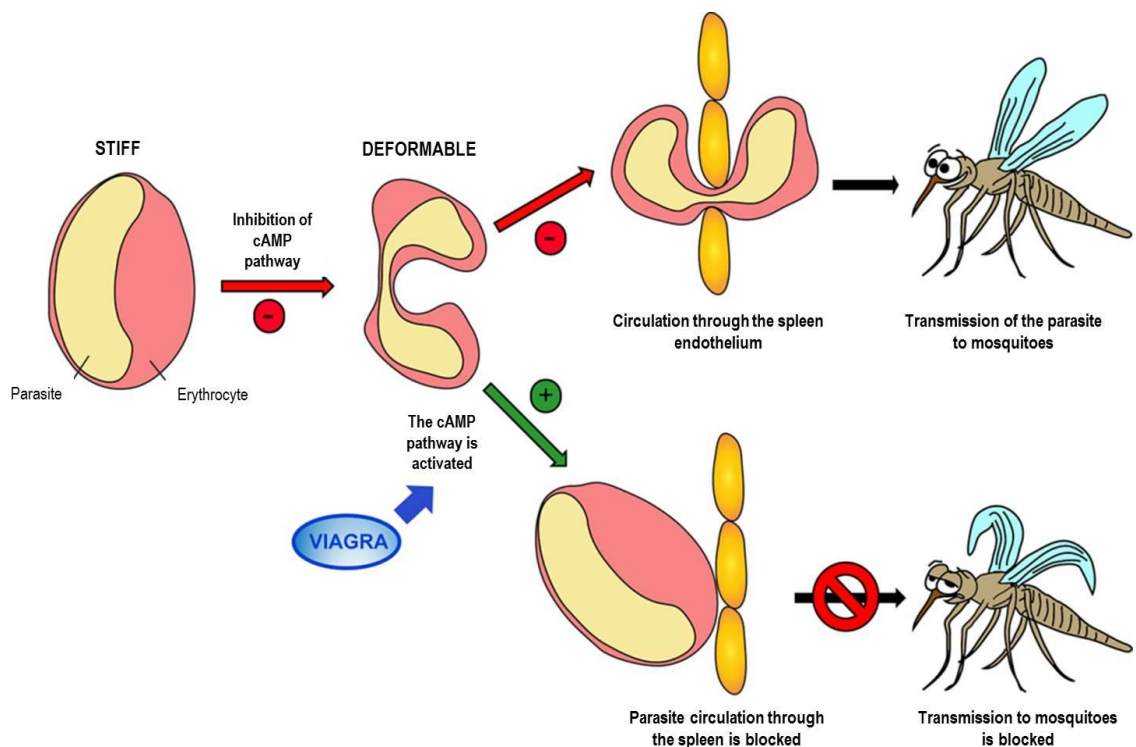
The sexual forms of the parasite develop in human erythrocytes sequestered in the bone marrow before they are released into the blood. They are then accessible to mosquitoes, which can ingest them when they bite (see the top of the image on page 2). But circulating erythrocytes — whether they are gametocyte-infected or not — are deformable, thus preventing their clearance via the spleen, which constantly filters the blood and only retains stiff, old or abnormal erythrocytes. However, gametocyte-infected erythrocytes can easily pass through the spleen and persist for several days in the blood circulation.

During a new study, the scientists thus sought to stiffen the infected erythrocytes. They showed that the deformability of gametocyte-infected erythrocytes is regulated by a signaling pathway that involves cAMP. When the cAMP molecules accumulate, the erythrocyte becomes stiffer. cAMP is degraded by the enzyme phosphodiesterase, whose action thus promotes erythrocyte deformability.

Using an *in vitro* model reproducing filtration by the spleen, the scientists were able to identify several pharmacological agents that inhibit phosphodiesterases and can therefore increase the stiffness of infected erythrocytes. One of these agents is sildenafil citrate, better known under its brand name of Viagra. The authors showed that this agent, used at a standard dose, had the potential to increase the stiffness of sexual forms of the parasite and thus favor the elimination of infected erythrocytes by the spleen.

This discovery could help find new ways to stop the spread of malaria in a population. Modifying the active substance in Viagra to block its erectile effect, or testing similar agents devoid of this adverse effect, could indeed result in a treatment to prevent transmission of the parasite from humans to mosquitoes.

This study involved the teams led by Catherine Lavazec and Gordon Langsley at the Institut Cochin and Institut Pasteur and David Baker's team at the London School of Hygiene and Tropical Medicine. It received support from the CNRS ATIP-Avenir program, INSERM, the Labex Gr-EX and Parafrap, the Fondation Inkermann and the Bill and Melinda Gates Foundation, in the context of a project in collaboration with Pierre Buffet's team at Université Pierre et Marie Curie.



The deformability of gametocyte-infected erythrocytes, facilitated when the cAMP pathway is inhibited, allows them to circulate freely through the spleen and remain accessible to mosquitoes in the blood circulation (top). The action of Viagra increases the stiffness of infected erythrocytes by activating the cAMP pathway, preventing their passage through the spleen endothelium and clearing the parasites from the blood circulation (bottom).



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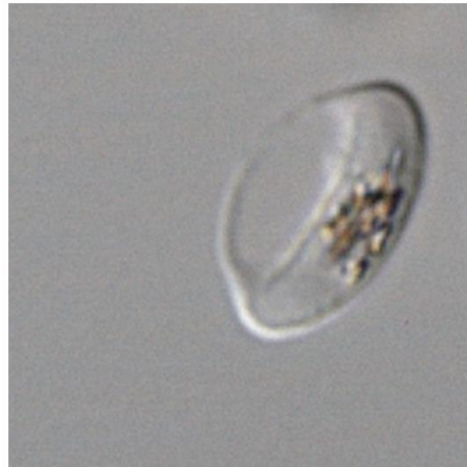
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Left: an infected erythrocyte changes its shape to pass through the spleen filter. Right: after treatment with a phosphodiesterase inhibitor such as Viagra, the infected erythrocyte is stiff.

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